CANADIAN THESES ON MICROFICHE

I.S.B.N.

THESES CANADIENNES SUR MICROFICHE

National Library of Canada
Collections Development Branch

Canadian Theses on
Microfiche Service

Ottawa, Canada
K1A 0N4

Bibliothèque nationale du Canada
Direction du développement des collections

Service des thèses canadiennes
sur microfiche

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us a poor photocopy.

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed.

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30. Please read the authorization forms which accompany this thesis.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

AVIS

La qualité de cette microfiche dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de mauvaise qualité.

Les documents qui font déjà l'objet d'un droit d'auteur (articles de revue, examens publiés, etc.) ne sont pas microfilmés.

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30. Veuillez prendre connaissance des formules d'autorisation qui accompagnent cette thèse.

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

NL-339 (r. 82/08)

Canada

0-315-08921-0

National Library of Canada
Bibliothèque nationale du Canada

32 Canadian Theses Division
Division des thèses canadiennes

Ottawa, Canada
K1A 0N4

56838

PERMISSION TO MICROFILM — AUTORISATION DE MICROFILMER

- Please print or type — Écrire en lettres moulées ou dactylographier

Full Name of Author — Nom complet de l'auteur
VITTORIO FARINA

Date of Birth — Date de naissance JUNE 8, 1953	Country of Birth — Lieu de naissance ITALY

Permanent Address — Résidence fixe
LUNGARNO PACINOTTI, 26
56100 PISA (ITALY)

Title of Thesis — Titre de la thèse
SYNTHETIC METHODOLOGIES BASED ON ORGANOSELENIUM AND ORGANOCOPPER CHEMISTRY

University — Université
UNIVERSITY OF ALBERTA

Degree for which thesis was presented — Grade pour lequel cette thèse fut présentée
Ph.D.

Year this degree conferred — Année d'obtention de ce grade 1982	Name of Supervisor — Nom du directeur de thèse DERRICK L.J. CLIVE

Permission is hereby granted to the NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

L'autorisation est, par la présente, accordée à la BIBLIOTHÈQUE NATIONALE DU CANADA de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans l'autorisation écrite de l'auteur.

Date Nov. 4, 1981	Signature Vittorio Farina

NL-91 (4/77)

THE UNIVERSITY OF ALBERTA

SYNTHETIC METHODOLOGIES BASED ON ORGANOSELENIUM AND ORGANOCOPPER CHEMISTRY

by

© VITTORIO FARINA

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND
RESEARCH IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
Spring, 1982

Microfilm

THE UNIVERSITY OF ALBERTA

RELEASE FORM

NAME OF AUTHOR: Vittorio Farina

TITLE OF THESIS: Synthetic Methodologies Based On Organoselenium and Organocopper Chemistry

DEGREE FOR WHICH THESIS WAS PRESENTED: Ph.D.

YEAR THIS DEGREE GRANTED: 1982

Permission is hereby granted to THE UNIVERSITY OF ALBERTA LIBRARY to reproduce single copies of this thesis and to lend or sell such copies for private, scholarly or scientific research purposes only.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

(signed) Vittorio Farina

PERMANENT ADDRESS:
Lungarno Pacinotti, 26
56100 Pisa, Italy.

DATED: November 2, 1981.

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled SYNTHETIC METHODOLOGIES BASED ON ORGANOSELENIUM AND ORGANOCOPPER CHEMISTRY submitted by Vittorio Farina in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

D. L. J. Clive
Supervisor

Martin Cowie

Karl R. Kopecky

Date: November 2, 1981.

TO PATTY AND SUSY

Abstract

This thesis deals with three subjects: the cyclofunctionalization of olefinic urethanes; the reactions of vinylsilanes with selenium electrophiles; and the reaction of cuprates with α,β-unsaturated aldehydes.

In the first part, an efficient and versatile synthesis of nitrogen heterocycles is described. Aliphatic and aromatic urethanes containing suitably positioned double bonds can be cyclized in good yields using benzeneselenenyl chloride in the presence of silica gel. The regio- and stereochemical implications of the reaction are also discussed.

In the second part, a functionalized vinylsilane is examined as a substrate for a selenium-induced ring closure, in an attempt to direct the regiochemistry of the cyclization process. It is found that the presence of a trimethylsilyl group on the double bond retards the ring-forming process in a significant way.

In the final part, the first efficient procedure for conjugate methylation of α,β-unsaturated aldehydes is described. It is shown that the species $Me_5Cu_3Li_2$ in ether or ether-pentane is a useful reagent for such a transformation, the proportions of 1,2-addition product being usually negligible in unhindered systems, contrary to the results observed with lithium dimethyl cuprate.

Other cuprates which can deliver a methyl group to enals in a conjugate fashion are also examined.

Acknowledgements

I would like to thank Dr. D.L.J. Clive for his invaluable help during the course of my studies.

I am also grateful to the Izaak Walton Killam Foundation for financial support in the form of a generous scholarship. Financial assistance from the H.H. Parlee Memorial Foundation, from the Alberta Heritage Foundation for Medical Research, and the Department of Chemistry of the University of Alberta is also gratefully acknowledged.

Finally, I wish to thank Jacki Jorgensen for typing this thesis.

TABLE OF CONTENTS

PAGE

ABSTRACT v

ACKNOWLEDGEMENTS vii

LIST OF TABLES x

ABBREVIATIONS xi

PART 1: CYCLOFUNCTIONALIZATION OF OLEFINIC URETHANES

INTRODUCTION 1

DISCUSSION

(A) Availability of the olefinic urethanes 7

(B) Cyclofunctionalization studies 10

PART 2: REACTIONS OF VINYLSILANES WITH SELENIUM ELECTROPHILES

INTRODUCTION 28

DISCUSSION 31

PART 3: ADDITIONS OF CUPRATES TO α,β-UNSATURATED ALDEHYDES

INTRODUCTION 38

DISCUSSION

(A) Availability of α,β-unsaturated aldehydes 43

(B) Cuprate additions to α,β-unsaturated aldehydes 48

EXPERIMENTAL PART

(A) General 74

PAGE

(B) Cyclofunctionalization of olefinic urethanes 79

(C) Reactions of vinylsilanes with selenium electrophiles 109

(D) Additions of cuprates to α,β-unsaturated aldehydes 119

REFERENCES AND NOTES 154

LIST OF TABLES

TABLE		PAGE
1	Cyclofunctionalization of olefinic urethanes in the absence of silica gel	5
2	Cyclofunctionalization of olefinic urethanes in the presence of silica gel	14
3	Reactions of various enals with $Me_5Cu_3Li_2$ and Me_2CuLi	54-55
4	Action of various cuprates on 2-cyclopentylidene propionaldehyde	63

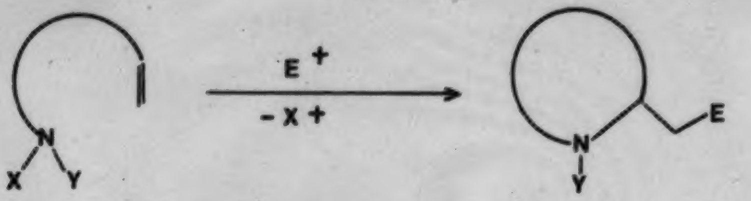
ABBREVIATIONS

S.M. = starting material
THF = tetrahydrofuran
HMPA = hexamethylphosphoric amide
VPC = vapor phase chromatography
PLC = preparative layer chromatography
TLC = thin layer chromatography
m-CPBA = *meta*-chloroperbenzoic acid
LAH = lithium aluminum hydride
DMF = dimethylformamide
LDA = lithium diisopropyl amide
DME = dimethoxyethane
Me = methyl
Pr = propyl
Ph = phenyl
Et = ethyl
Bu = butyl
Py = pyridine
DMSO = dimethylsulfoxide

PART 1: CYCLOFUNCTIONALIZATION OF OLEFINIC URETHANES

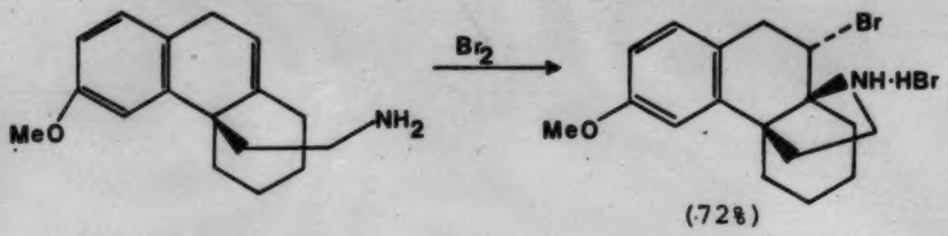
INTRODUCTION

Nitrogen heterocycles are widespread in nature[1] and consequently synthetic methods for their synthesis are important. One approach to these systems involves, as a key step, formation of a carbon-nitrogen bond with concomitant ring closure, as in Eq. (1).



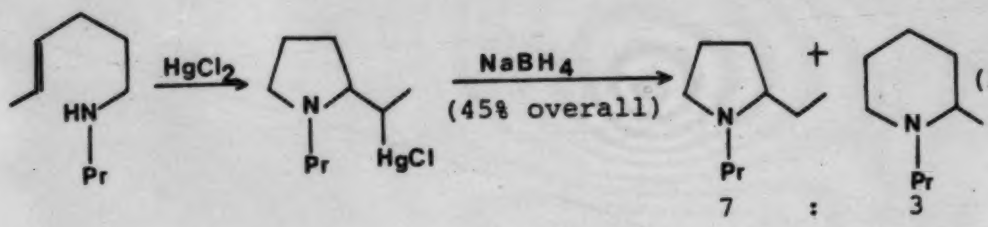
(1)

Eq. (1) shows only one of the two conceivable products, the other one having the larger ring size, and the regioselectivity in these processes will generally depend on the electrophile used, the substituents on the nitrogen, the length of the carbon chain connecting the two cyclizing termini,[2] and possibly other factors such as solvent, temperature or particular features of the molecule being cyclized. Halogens have been known as effective reagents in this respect for almost a century[3a] and have been employed often in the synthesis of complex molecules, as for example in the reaction shown in eq. (2).[3b]


MeO
NH$_2$
Br$_2$
Br
NH·HBr
MeO
(72%)

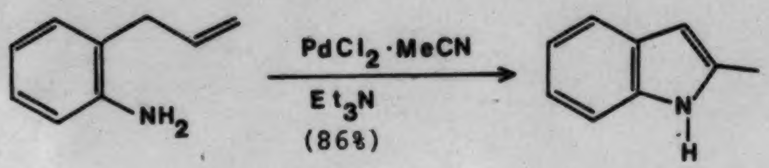
(2)[3b]

Another reagent that has been investigated thoroughly as a cyclizing agent for unsaturated amines is mercuric ion[4] [eq. (3)].


HN
Pr
HgCl$_2$
N
Pr
HgCl
NaBH$_4$
(45% overall)
N
Pr
+
N
Pr
7 : 3

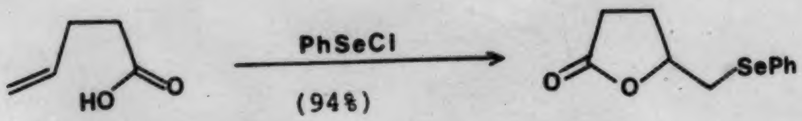
(3)

The intermediate organomercury compounds are usually very labile[4a] and are reduced in situ with sodium borohydride.[5] A limitation to this methodology is that usually both possible ring sizes are obtained, owing to fast rearrangement during the reduction.[6] A recently described methodology using palladium electrophiles[7] provides a route to indoles:


PdCl2·MeCN
Et3N
(86%)
NH2
N
H

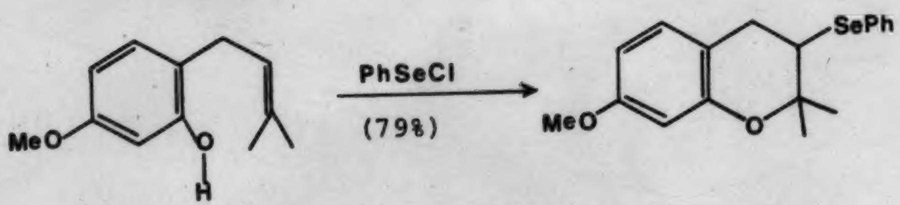
(4)

Selenium electrophiles, especially the commercially available benzeneselenenyl chloride[8] have been used to effect a number of cyclizations[9] in excellent yields, as shown in eq. (5)-(7).


HO
O
PhSeCl
(94%)
O
O
SePh

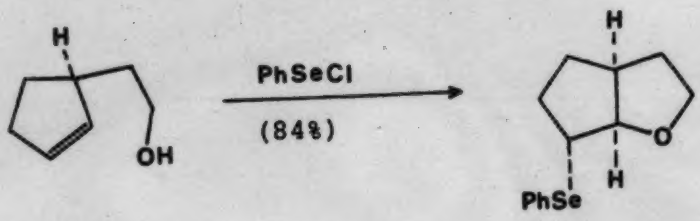
Ref: 9c

(5)


MeO
O
H
PhSeCl
(79%)
SePh
MeO
O

Ref: 9a

(6)


H
OH
PhSeCl
(84%)
H
O
H
PhSe

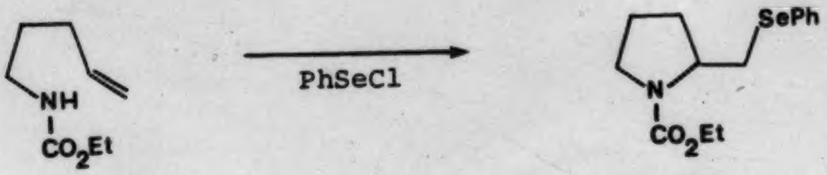
Ref: 9d

(7)

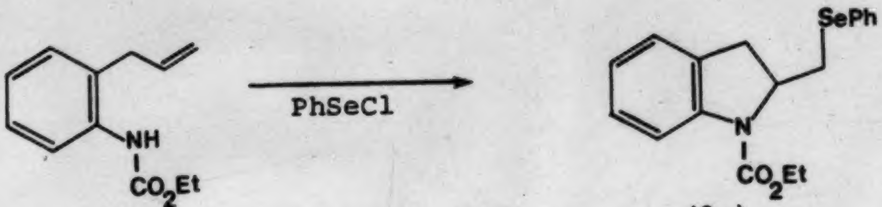
With the aim of extending this methodology to the realm of unsaturated amines, it had been discovered in this laboratory[10] that amines have to be masked in order to observe ring closure, and that the urethane functionality is well suited in this respect. Four representative amines had been cyclized in fair yields, simply by adding benzeneselenenyl chloride to a dichloromethane solution of the amine, containing in some cases one equivalent of silver trifluoroacetate (see Table 1). The yields were not excellent, but several features seemed encouraging about this reaction: contrary to the mercuric ion-promoted reaction, only one ring size was observed here, namely the one resulting from an *exo*[2] process. The selenium-containing products were quite stable (in fact, they could be distilled under reduced pressure) and were cleanly reduced to the parent hydrocarbons using triphenyltin hydride,[11] in such a way as to confirm the assigned structures and at the same time making the synthetic method more complete and useful. The interest toward the above scheme is increased by the considerable number of synthetic transformations that can be carried out on the phenylseleno group (for this reason the cyclization process has been named *cyclofunctionalization*[9a]): among them, most notably, selenoxide fragmentation[12] (to yield olefins) is a powerful and widely used synthetic

Table 1. CYCLOFUNCTIONALIZATION OF OLEFINIC URETHANES IN THE ABSENCE OF SILICA GEL.

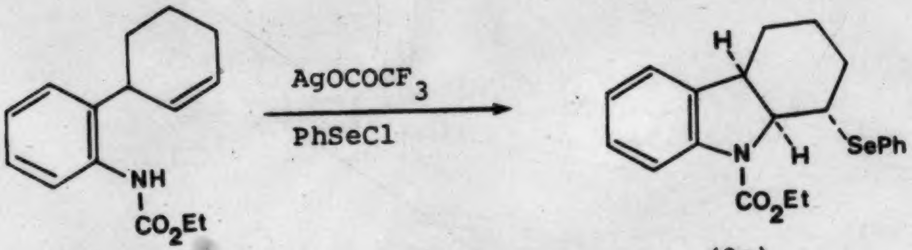
YIELD:[10]


NH
CO2Et
PhSeCl
SePh
N
CO2Et

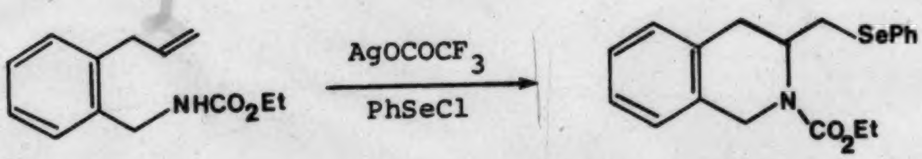
(1) → (1a) 77%


NH
CO2Et
PhSeCl
SePh
N
CO2Et

(2) → (2a) 73%


NH
CO2Et
AgOCOCF3
PhSeCl
H
H
SePh
N
CO2Et

(3) → (3a) 59%


NHCO2Et
AgOCOCF3
PhSeCl
SePh
N
CO2Et

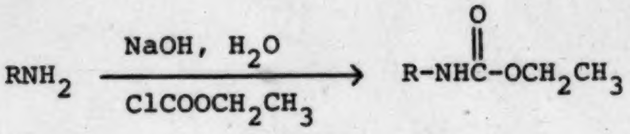
(4) → (4a) 52%

method;[13] alkyl phenyl selenides can be deprotonated and alkylated with some difficulty[14] and, more importantly, selenoxides, formed in situ, can be cleanly deprotonated and treated with electrophiles, to provide versatile routes to allylic alcohol and olefins;[15] the phenylseleno group can be converted into other functional groups, such as halides,[16] or be replaced by an alkyl group[17] using Grignard reagents. Consequently, it appeared desirable to study the reaction in further detail with the aim of increasing the yields to a preparatively useful level and of confirming the postulated "anti" stereochemistry of addition at the double bond.

DISCUSSION

(A): Availability of the olefinic urethanes.

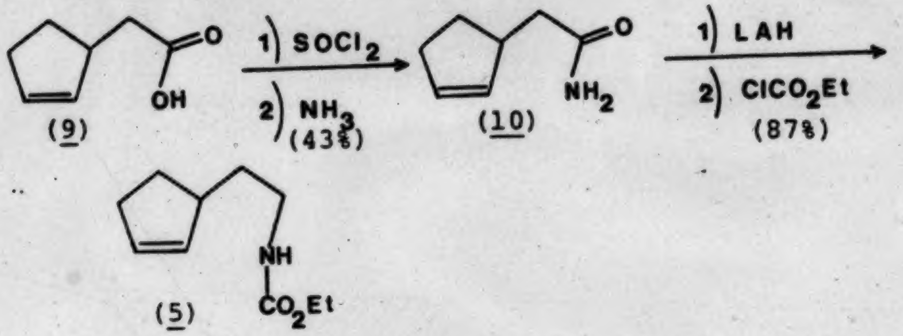
The olefinic urethanes required for this study were prepared from the parent primary amines by the standard Schotten-Baumann[18] method:



$$RNH_2 \xrightarrow[ClCOOCH_2CH_3]{NaOH,\ H_2O} R\text{-}NH\overset{\overset{O}{\|}}{C}\text{-}OCH_2CH_3 \qquad (8)$$

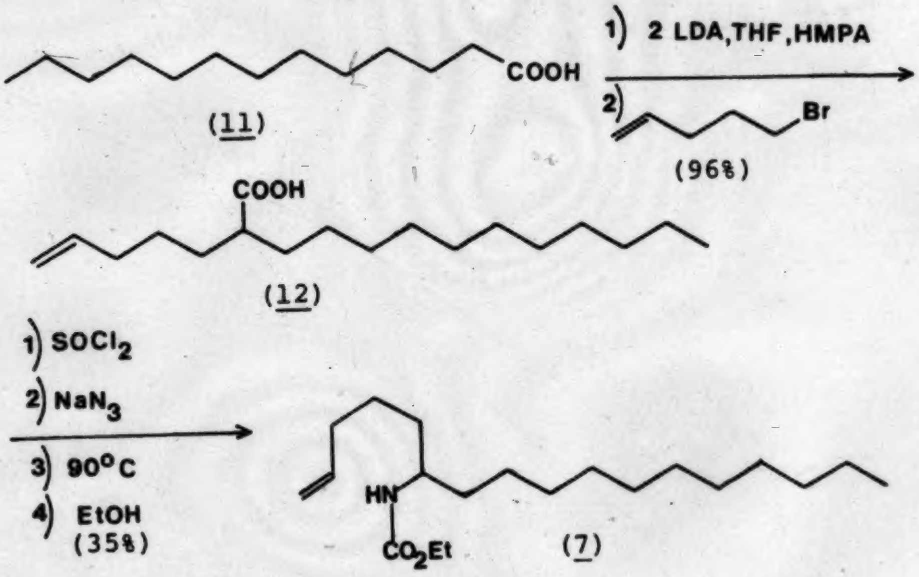
The yields for each compound are indicated in Table 2 (p. 14). They refer to the acylation step, except for the preparation of (4), (5), (6) and (7), in which the urethanes were obtained directly, without the isolation of the parent amine. In this case the yields refer to the final step of the preparation. Aliphatic amines can usually be obtained in good yields using the classical Gabriel synthesis,[19] and (1) was prepared in this way, using the published procedure.[20]

Another convenient route to δ,ε-unsaturated amines is *via* the parent amides, easily obtainable from γ,δ-unsaturated carboxylic acid, in turn readily available by malonic ester synthesis;[21] (5) and (6) were made by this route, e.g.


1) SOCl$_2$
2) NH$_3$
(43%)
1) LAH
2) ClCO$_2$Et
(87%)
OH
NH$_2$
NH
CO$_2$Et
(9)
(10)
(5)

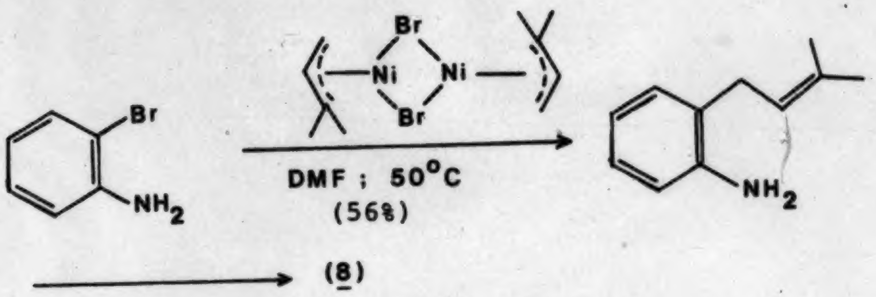
(9)

Urethane (7) was easily prepared in two steps, namely alkylation of a carboxylic acid dianion[22] followed by Curtius rearrangement;[23] for this rearrangement refined experimental procedures have been published recently;[24] we have chosen to employ classical conditions owing to considerations of reagent availability. In spite of the low yield, (7) could be obtained in multigram quantities without problems.


COOH
(11)
1) 2 LDA,THF,HMPA
2)
Br
(96%)
COOH
(12)
1) SOCl$_2$
2) NaN$_3$
3) 90°C
4) EtOH
(35%)
HN
CO$_2$Et
(7)

(10)

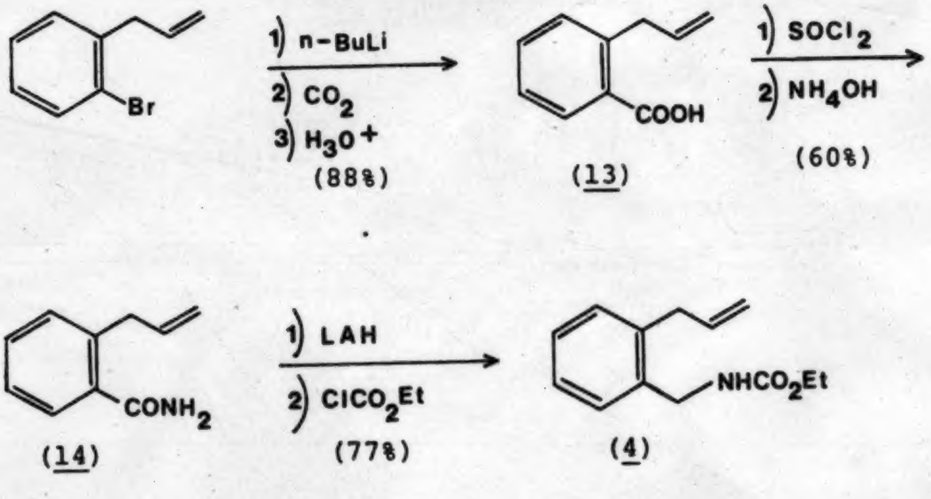
For the preparation of unsaturated anilines, a convenient method has become available recently,[7] using π-allyl nickel methodology.[25] Both (3) and (8) (See Table 2, p. 14) were made by this route, e.g.


Br
NH$_2$
Br
Ni
Ni
Br
DMF ; 50°C
(56%)
NH$_2$

(11)

(8)

Compound (4) was also made via this route, but it was found convenient, in order to obtain multigram quantities of the compound, to devise a new synthesis of the material according to a more classical scheme, as shown in eq. (12).


Br
1) n-BuLi
2) CO$_2$
3) H$_3$O+
(88%)
COOH
1) SOCl$_2$
2) NH$_4$OH
(60%)
CONH$_2$
1) LAH
2) ClCO$_2$Et
(77%)
NHCO$_2$Et

(13)

(14)

(4)

(12)

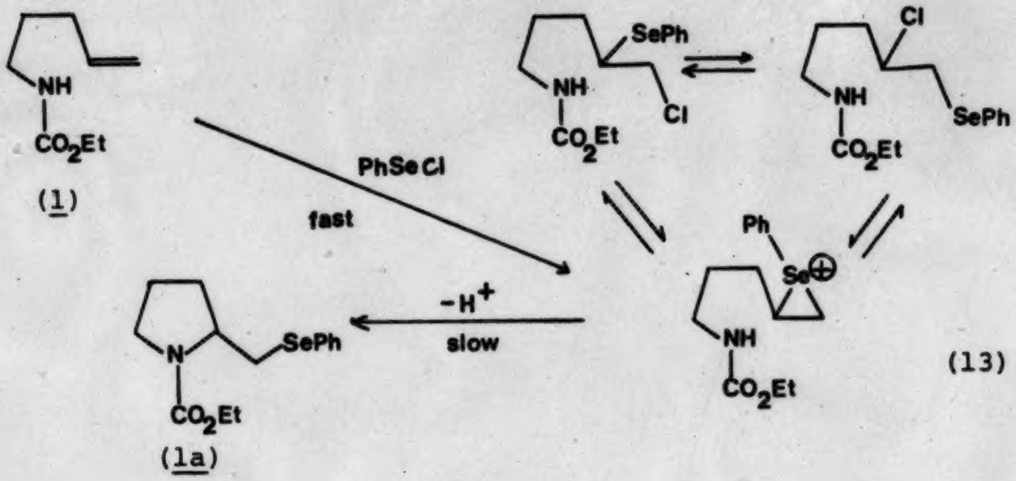
Finally, (2) was made according to a published procedure,[26] involving nitration of allylbenzene, separation of the isomers (ortho- and para-allyl nitrobenzene) by spinning-band distillation, followed by reduction. Other available methodologies, such as the ones based on the amino-Claisen rearrangement,[27] seem to be somewhat limited,[7] due to the rather severe acidic conditions that are necessary to promote the allylic shift. It is clear that an adequate array of synthetic routes exists for the preparation of unsaturated amines, and especially the new, versatile π-allyl nickel methodology adds potential to our cyclization route.

(B): Cyclofunctionalization Studies.

When we repeated the original cyclization experiments[10] on urethane (1), in search of possible side products, we failed to isolate materials other than (1a) and, by column chromatography, fractions that were mixtures of (1) and (1a). It seemed that the reaction did not go to completion, in spite of the observation that the red-brown color of benzeneselenenyl chloride was discharged instantly at -75°C, indicating that some reaction was taking place. A TLC taken after a few minutes at room temperature showed a spot due to (1a) and a considerable streaking that suggested the presence of some unstable species. We then decided to carry out the reaction in a ^{1}H-NMR probe, using dry $CDCl_3$ as a solvent, confident that chloroform and dichloromethane are similar enough to allow us to extend our observations to the preparative runs.

When PhSeCl was added to the starting urethane (1) at -50°, the signals due to the olefinic protons rapidly disappeared, and also the higher field range (δ 2.0-4.0) changed drastically, with the appearance of new signals: the spectrum slowly changed further with temperature increase (up to room temperature), but none of the product (1a) was observed even after several hours at room temperature. Column chromatography at this stage did provide, however, (1a) in modest yield. Even though the NMR spectra were too complex to be amenable to any detailed interpretation, one important conclusion could be drawn from the study: there is an initial reaction of benzeneselenenyl chloride with the substrate, but the product is formed only later. Furthermore, the silica gel used in the column appears to accelerate the decomposition of the initial adduct(s), to give both starting material and cyclized products. Our interpretation is shown below.[28]

We then decided to carry out the reaction in the presence of silica gel. Due to the variable composition



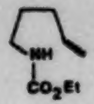
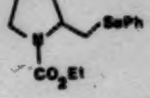
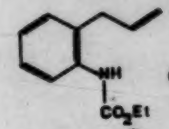
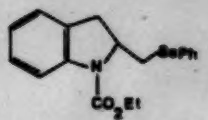
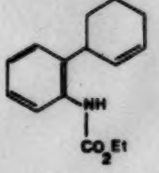
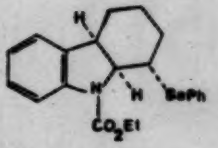
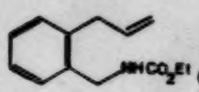
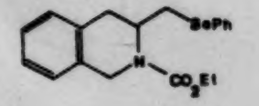
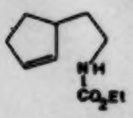
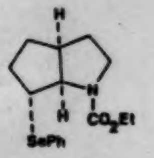
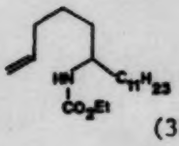
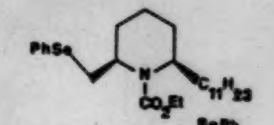
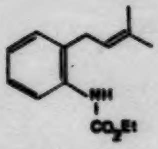
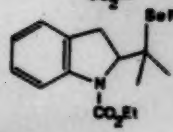
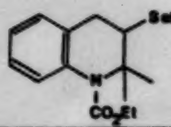
(13)

of these gels[29a] and the uncertainty about their water content,[29b] it was difficult at this stage to make a choice of particle size and drying procedure, and to predict whether or not the adsorbant would react with (and destroy) our selenium reagent. We arbitrarily decided to use silica gel for PLC (Merck) that had been subjected to an overnight drying period at 130°C.

In our first run we added the silica gel to the preformed urethane-benzeneselenenyl chloride adduct at room temperature, but later we found no difference if the silica gel was present from the beginning, and we then used this simpler procedure. Under the influence of silica gel, the reaction was over after 1.5 h at room temperature, as evidenced by TLC, which showed a single spot (apart from some diphenyl diselenide) and no streaking, as well as from an NMR spectrum of a portion withdrawn and evaporated prior to chromatography. The urethane (1a) was obtained analytically pure in 93% yield. After this successful attempt, we tried to extend the above observations to urethanes (2)—(4), hoping that the yields would be as good in these cases. Periodical TLC examination of the reaction mixtures showed that cyclization of the aniline derivatives was somewhat slower than in the case of (1), and we increased reaction times routinely to 16-24 h. The yields of analytically pure, cyclized urethanes, as shown in Table 2, were consistently better than 80% and, judging by the TLC of the crude mixture, the reactions were extremely clean. We also investigated another adsorbant, namely alumina (which had been pre-dried in the same way), and the yield, in the case of (2), was equally good.

Products (1a)-(4a) had already been characterized by tin-hydride reduction.[10] The stereochemistry of (3a) was tentative, assigned on the basis of a supposed anti mode of addition. As additional confirmation of the five-membered ring nature of (1a), we carried out a

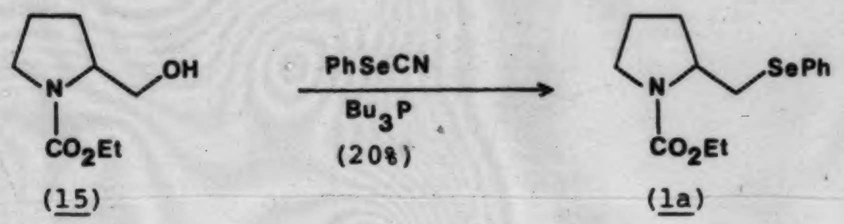
Table 2. CYCLOFUNCTIONALIZATION OF OLEFINIC URETHANES IN THE PRESENCE OF SILICA GEL[a]

	Urethane	(Yield[b])		Product	Reaction Time (h)	Yield
(1)		(89%)	(1a)		1.5	93%
(2)		(84%)	(2a)		24	85%
(3)		(86%)	(3a)		24	82%
(4)		(72%)[c]	(4a)		16	87%
(5)		(87%)[d]	(5a)		16	94%
(7)		(35%)[e]	(7a)		40	84%
(8)		(90%)	(8a) (8b)	  [f]	70	76%

---

[a] Yields refer to isolated material. [b] The urethanes were prepared in the yield shown from the corresponding amines, except where noted. [c] Yield refers to the reduction-acylation of 2-allyl benzamide. [d] Yield refers to the reduction-acylation of (2-cyclopentenyl)acetamide. [e] Yield refers to the Curtius rearrangement of 2-undecylhept-6-enoic acid. [f] The products were formed in a ratio of ca. 1:1 (NMR). In this run propylene oxide was used as an acid trap.

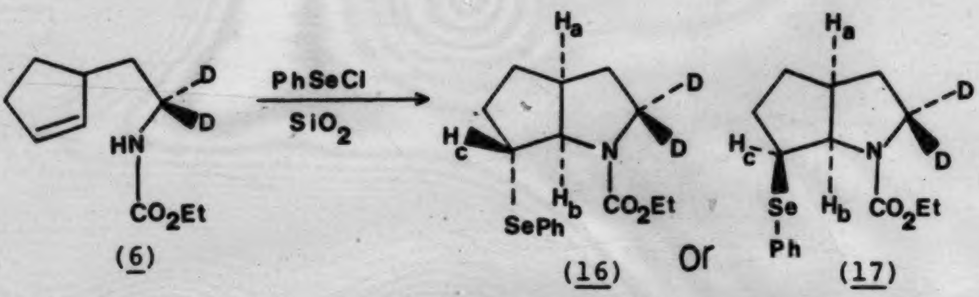
preparation of this material *via* another route, using the general method of conversion of primary alcohols into alkylarylselenides.[30] This authentic material was


OH
N
CO2Et
(15)
PhSeCN
Bu3P
(20%)
SePh
N
CO2Et
(1a)

(14)

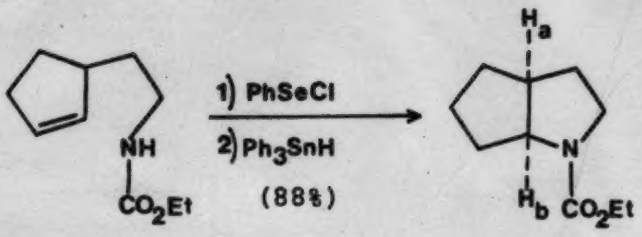
identical (IR, NMR, TLC) to our synthetic (1a).[31] In order to confirm the postulated stereochemistry of ring closure, we chose to study the octahydro cyclopenta[b] pyrrole system, which, due to its rigidity, should be well suited to a coupling constant study in the ^{1}H-NMR.

For the purpose of simplifying the NMR spectrum, we carried out our studies on the 1,1-dideutero analogue of (5), namely (6), which was obtained by lithium aluminum deuteride reduction of amide (10). The *cis* ring


D
D
HN
CO2Et
(6)
PhSeCl
SiO2
Ha
D
Hc
N
D
SePh
Hb
CO2Et
(16)
or
Ha
D
Hc
N
D
Se
Ph
Hb
CO2Et
(17)

(15)

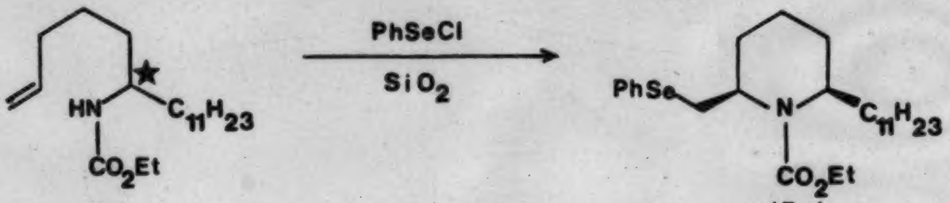
junction had already been established by converting the



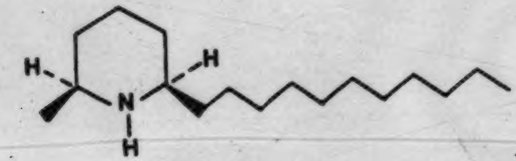
(5) (18) (16)

ring-closure product of (5), (5a) into (18). This was then shown to be identical to an authentic sample prepared from the known cis-octahydrocyclopenta[b]pyrrole. In (17) the coupling constant between H_b and H_c is expected to be 7-8 Hz by inspection of Dreiding models, while in the case of (16) such coupling should be much smaller (ca. 1.5 Hz).[32] The structure (17) was ruled out by the observation that in the ring-closure product from (6), H_b showed a doublet (J_{ab} = 7 Hz) with a width at half-height of 4 Hz, indicating $J_{ac} \leq$ 4 Hz, thus confirming the structure shown for (5a). This establishes as anti the mode of addition across the double bond in this particular ring-closure process, and we are confident that this conclusion is general for reactions employing our experimental conditions.

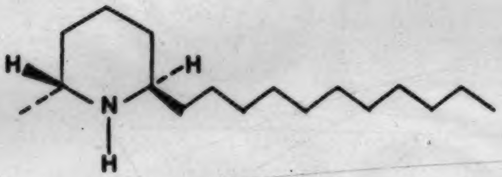
The experiments on (7) illustrate a further stereochemical feature of our reaction.


PhSeCl
SiO$_2$
HN
C$_{11}$H$_{23}$
CO$_2$Et
PhSe
N
C$_{11}$H$_{23}$
CO$_2$Et

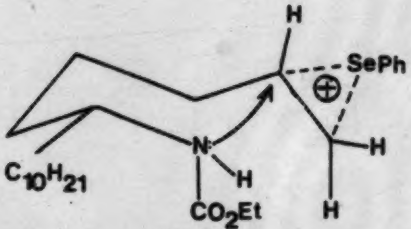
(7) (7a) (17)



(19)



(20)

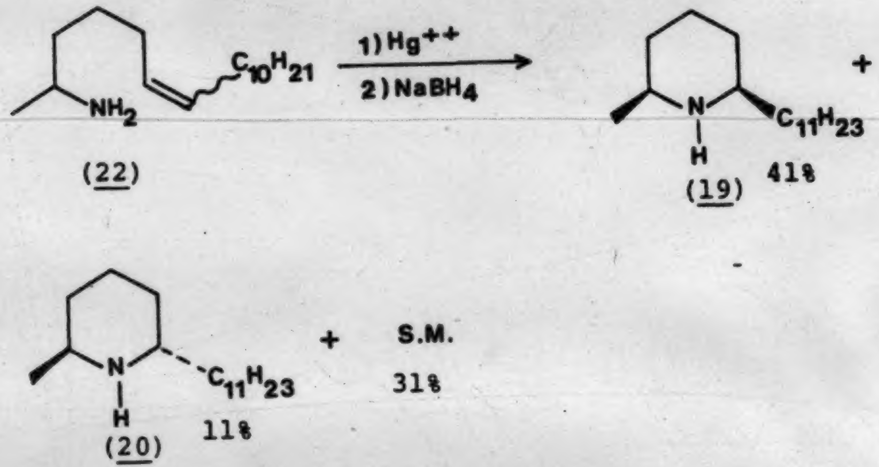

H
SePh
⊕
N
H
H
H
C$_{10}$H$_{21}$
CO$_2$Et

(21)

In this case, where the urethane bears an asymmetric center α to the nitrogen, the newly created asymmetric center in (7a) is formed with complete cis stereoselectivity, as shown by tin hydride reduction (96% yield) and hydrolytic deprotection (93.4%) to the known[33a] amine (19)[33b] which is the C-2 epimer of a natural substance, solenopsin, (20), isolated from the venom of the

African fire ant solenopsis saevissima.[33a]

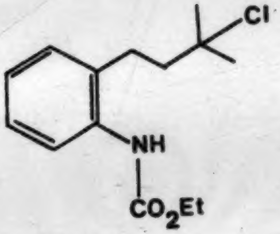
This result is in contrast with the mercuric-ion promoted ring-closure, which was used in a recent synthesis of solenopsin,[34] as shown in eq. (18).



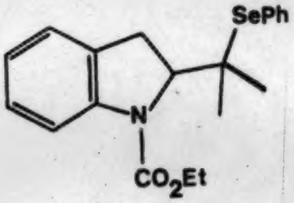
(18)

Thus, our reaction is more stereoselective, at least in this particular system,[35] than the one using mercuric salts, and we rationalize the result by postulating that in the transition state the alkyl group prefers to occupy an equatorial position, as in (21). It is however, possible, in principle, to obtain a mixture of cis and trans 2,6-dialkylpiperidines by base-catalyzed equilibration of the parent nitrosamine, followed by removal of the nitroso group.[36]

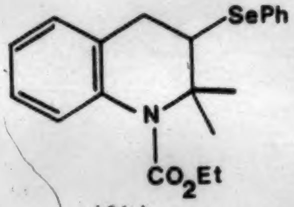
The reaction of (8) with benzeneselenenyl chloride was far more complex than the other cases: after some experimentation, we found that good yields in the cyclization could be obtained by adding an acid scavenger such as propylene oxide to the reaction mixture. Although the hydrogen chloride formed as a side product during cyclization was not harmful, at least in the presence of silica gel, in the cases (1)—(7), it clearly caused some problems in the case of (8). Among the many side products, only one could be isolated pure. It was identified as (23) (14% yield). When the acid trap was used, however, the reaction was rather clean, no (23) was detected, and two cyclized products, (8a) and (8b), were isolated in good yield. Although they could not be separated by chromatography, their tin-hydride reduction products, (24) and (25) were separable (VPC, APIEZON column) and their characterization confirmed the structures



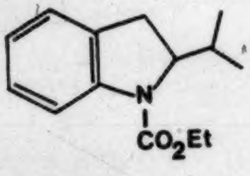
(23)



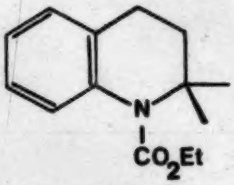
(8a)



(8b)

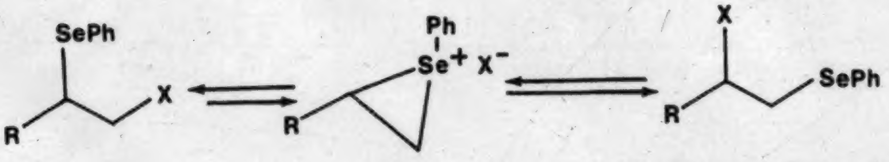


(24)



(25)

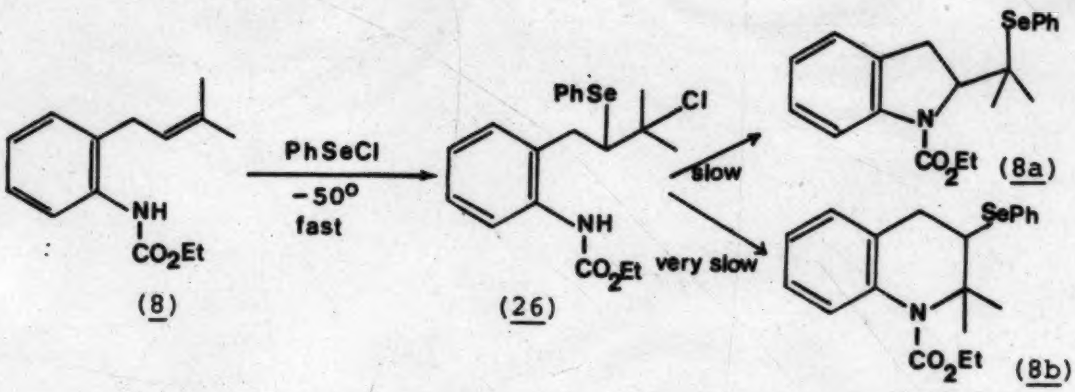
assigned to (8a) and (8b). As this was the only case in which we observed two competitive processes of ring-closure (5-exo and 6-endo),[2] we were led to investigate the reaction further, with the aim of discovering whether the product distribution was of kinetic origin or whether some equilibration process was involved. A similar study on phenylselenolactonization[9c] carried out in our laboratory had already shown examples in which the kinetically favored 6-endo closure is followed by rearrangement to the more stable 5-membered ring lactone. We wondered whether a similar phenomenon was occurring in this case, although it has been shown[28] that the rate of equilibration of olefin——PhSeX adducts (X = halide, acetate) depends [eq. (19)] on the tendency of X to



(19)

Kinetic Thermodynamic

function as a leaving group, and in the present case ($X = R\ddot{N}COOCH_2CH_3$) such a possibility seems quite unfavorable. Our first approach was to carry out an NMR study: When the reaction was performed in dry $CDCl_3$ at -50°C in an NMR probe, we observed immediate reaction of



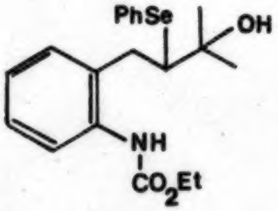
(20)

benzeneselenenyl chloride with the double bond of (8) [as in the NMR study with (1)].

In this particular case the NMR spectrum could be interpreted and the signals were consistent with the presence of only one species at -50°C after *ca*. 1 h, namely (26). The proton α to the selenium atom showed a clean doublet at δ 3.65 with $J = 15$ Hz (coupling with the other proton, on the basis of the width at half-height is $\leq$ 2 Hz), while the benzylic protons gave, respectively, a doublet at δ 3.19 (geminal coupling, 12 Hz) and a doublet of doublets at δ 2.81 ($J_1 = 15$ Hz, $J_2 = 12$ Hz). The rest of the spectrum was consistent with the assignment. No change occurred when the temperature was raised to 25°C and kept at this value for 2 h. After *ca*. 3 h some other signals became evident, especially the ones due to (8a). After *ca*. 15 h the mixture seemed to consist of a 7:3 mixture of (26) and (8a), but by then both the quality of the spectrum (due to particle formation) and the composition of the mixture deteriorated (i.e., side products were observed). However, (8b) was not detected. The reaction seemed to have stopped and, after a total of 106 h at room temperature, at least 50% of the material still remained uncyclized (NMR observation after filtration of the mixture and evaporation). Compound (8a) was still the predominant product, and (8b) was detectable in small amounts. Thus the reaction could not be followed to completion, but it appeared obvious that the initial rate of formation of (8a) was higher than that of (8b), and consequently we were led to believe that (8a) is the kinetic product, and the 1:1 mixture finally obtained in preparative runs arises from a silica gel-catalyzed equilibration. This seemed to be confirmed by some equilibration experiments in which crude samples of (8a) were isolated and shown to produce variable amounts (never above 30% of the total cyclized material) of (8b) upon stirring over silica gel in dichloromethane or chloroform. The above samples were, however, very crude, and it was possible that some other species rearranged to (8b),[37] and so we sought a clear proof for the postulated equilibration.

When the reaction was carried out at -75°C for 1—2 h, the mixture briefly taken to room temperature and chromatographed, mixtures of (8a) and (8b) in which (8a) predominated could be obtained in variable yields, depending on the chromatographic details[38] (elution time, column size, adsorbant, eluant).

Since we know from the NMR study (if extrapolation of the data in chloroform can be made to the runs in dichloromethane), that soon after mixing only (26), the benzeneselenenyl chloride-urethane adduct, is present in solution, it follows that when (26) is applied onto silica gel in dichloromethane, the adduct decomposes to produce preferentially (8a), smaller amounts of (8b), traces of starting urethane, and a few other minor products. Typically, a 60% yield of (8a)—(8b) mixture is obtained. When, however, a mixture of heptane and ethyl acetate is used as a solvent for the chromatography (flash[39] technique was used), the main decomposition pathway is toward starting material, diphenyl diselenide, and a new product, in ca. 50% yield, identified as the "PhSeOH" adduct (27) on the basis of its NMR and



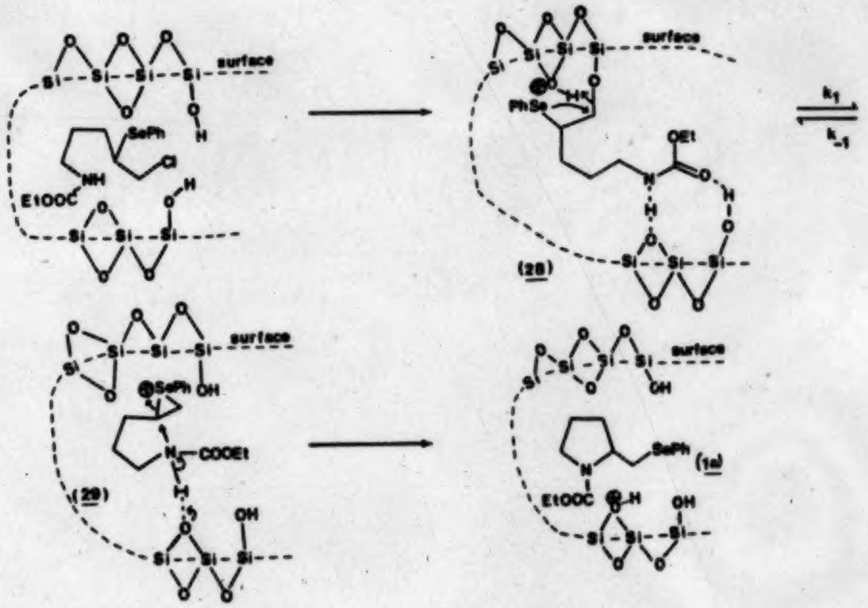
(27)

mass spectra.

If the reaction is allowed to proceed overnight (i.e., ca. 30% of the five-membered ring product is allowed to form) and the mixture then applied to the column, both dichloromethane and ethyl acetate—heptane solvent systems give appreciable yields (50-60%) of mixtures of (8a) and (8b), in which (8a) predominates. However, (8b) is present in substantial proportion (typically 30%). We briefly investigated alumina as a catalyst, but after routine overnight stirring we isolated only starting urethane (8) and observed by TLC much diphenyl diselenide. Evidently, alumina favors decomposition of adduct (26) to (8) and benzeneselenenyl chloride, which is slowly destroyed due to the protic nature of the surface (or by effect of the adsorbed water). In fact, chromatography of reaction mixtures (briefly run in the absence of a solid catalyst) on alumina gave mainly unreacted (8).[38] Finally, when a pure (TLC, NMR) 3:1 mixture of (8a) and (8b) was stirred at room temperature in dichloromethane in the presence of silica gel (conditions similar to our preparative run, see experimental) no rearrangement to the supposed 1:1 thermodynamic mixture was observed. The initial composition was instead observed even after 75 h. This mixture was also thermally stable at 200°C (during Kugelrohr distillation). We must conclude that probably all the mixtures isolated in the different runs are kinetic mixtures, the different compositions arising from a complex mechanism. We summarize our observations as follows: in the presence of dry silica and propylene oxide as an acid trap, (8a) and (8b) are formed at approximately the same rate to afford a 1:1 mixture of 5- and 6-membered ring urethanes. This, or any other, mixture with different proportions of (8a) and (8b) does not change in composition when stirred in the presence of silica gel. The rate of formation of (8a), however, seems to be, at least initially and in the absence of propylene oxide, faster than the rate of formation of (8b), both in dichloromethane solution and in the chromatographic column. It is likely that the kinetics of the reaction are quite complex, and the hydrogen chloride formed as a side product plays a role in the unusual effects observed. A further complication is introduced by the presence of silica gel (either *in situ* or in the column during purification by chromatography), which presumably catalyzes to a different extent most of the single steps involved in the overall reaction.

The overall catalytic effect of silica gel is not easy to account for; organic reactions at alumina surfaces have been reviewed[40] and it is appreciated that much further work is needed before solid supports can be used systematically in organic synthesis in a rational way.

Two roles of catalytic surfaces have been suggested: one is of entropic nature:[41] the surface would lower the entropy of activation when reacting species are adsorbed in proper position and orientation for chemical reaction. In our case, however, we expect this effect to be small, since in short-chain ring-closure reactions the entropy of activation is rather small.[42] Another effect is to activate one (or both) of the reagents for chemical reaction. In our case we can postulate that both the acidic (silanol bonds) and basic (siloxane bonds) sites[29a] of



Scheme 1

the surface have a catalytic effect. They might help in the removal of the proton on the nitrogen during (or prior to) cyclization, and they might speed up the formation of the presumed reactive species, the seleniranium ion (28), by readily removing the chloride ion from the initial adduct. The process (28) ⇄ (29) may also be catalyzed as shown in Scheme 1, and consequently, the overall cyclization process is facilitated.

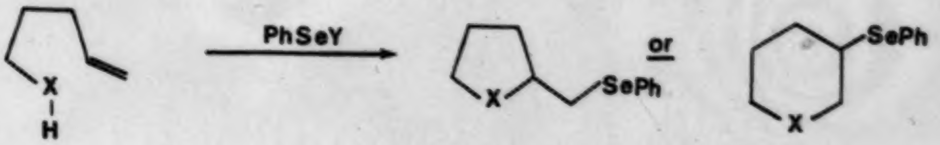
Finally, the problem of removing the ethoxycarbonyl protecting-activating group deserves a brief comment. As shown by the transformation (7a) → (19), hydrolysis (see p.17) of the urethane group requires harsh conditions. A solution to this problem might be offered by the recently introduced trimethylsilyl iodide reagent[43] and, in principle, amines as final products can be obtained also by using more easily removable alkoxycarbonyl protecting groups[44] such as the benzyloxy and the *t*-butyloxy groups, which can be cleaved under fairly mild conditions.

To conclude, the silica gel promoted cyclofunctionalization of unsaturated urethanes constitutes a reliable, simple and efficient route to nitrogen heterocycles. When the double bond is not heavily substituted, 5-*exo* processes are favored over 6-*endo* and 6-*exo* over 7-*endo*. In the cases of more substituted olefins, however [as in (8)], mixtures of the two possible products can be produced.

PART 2: REACTIONS OF VINYLSILANES WITH SELENIUM ELECTROPHILES

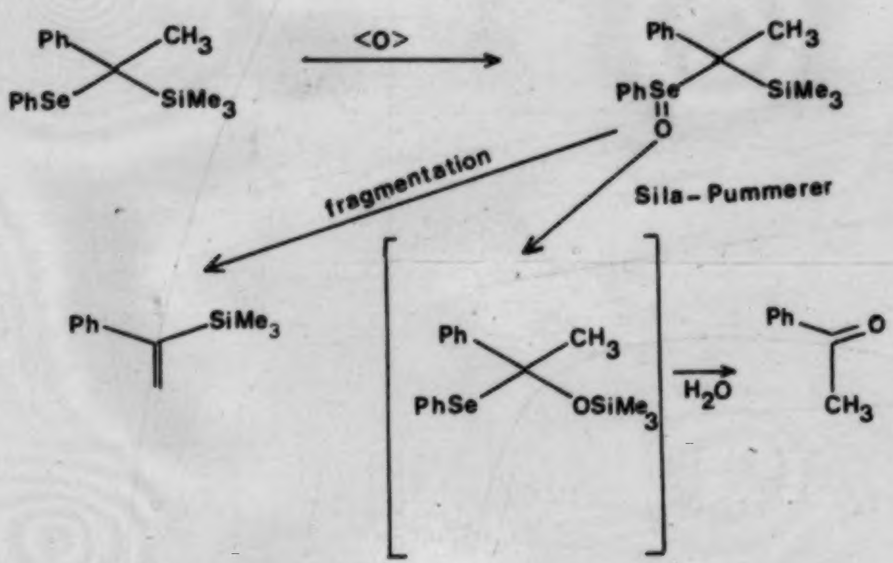
INTRODUCTION

From the chemistry discussed in part 1 of this thesis, it is clear that it would be very useful to be able to direct the cyclofunctionalization process[9a] toward either one of the olefinic termini, as shown in eq. (21) for the specific case of 5-*exo* versus 6-*endo*[2] competition.



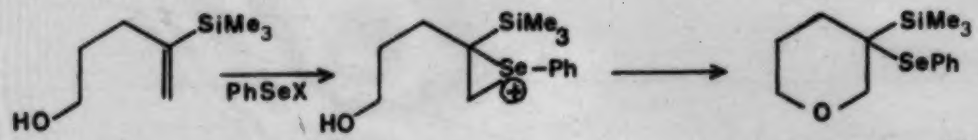
(21)

For example, in the case of unsaturated alcohols (X = O), it is known[9d] that 5-*exo* closure is usually selectively observed. This makes the 6-membered ring product hardly accessible, and we thought that it would be useful to explore the possibility of producing either one of the two isomeric products by placing a suitable substituent at a specific carbon atom of the double bond. Our choice of such a substituent was the trimethylsilyl group,[45] which is known to stabilize a positive charge (and presumably an incipient positive charge[46]) on a carbon atom β to it.[47] We also thought that such a group could be easily manipulated after the cyclization, in conjunction with the phenylseleno group. It is known, for example, that α-silyl selenides on oxidation undergo competitive sila-Pummerer rearrangement and selenoxide fragmentation[48] [eq. (22)].

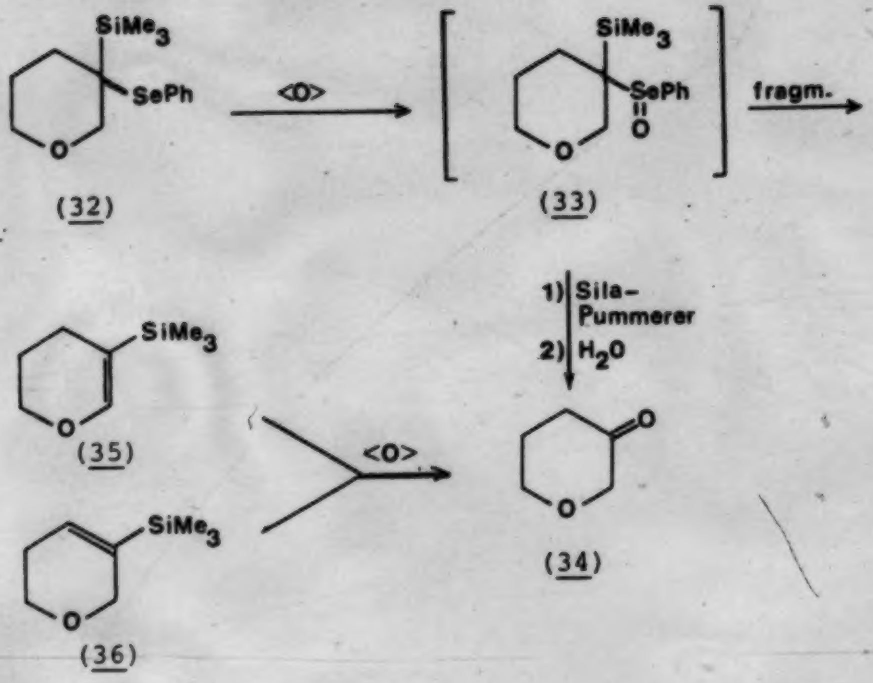

Ph
CH3
PhSe
SiMe3
<O>
Ph
CH3
PhSe
O
SiMe3
fragmentation
Sila-Pummerer
Ph
SiMe3
Ph
CH3
PhSe
OSiMe3
H2O
Ph
O
CH3

(22)

In any event, the fragmentation products are convertible, using known chemistry,[45] into the sila-Pummerer rearrangement product. What we were planning to accomplish is summarized in equations (23) and 24).


SiMe3
HO
PhSeX
SiMe3
Se-Ph
HO
SiMe3
SePh
O

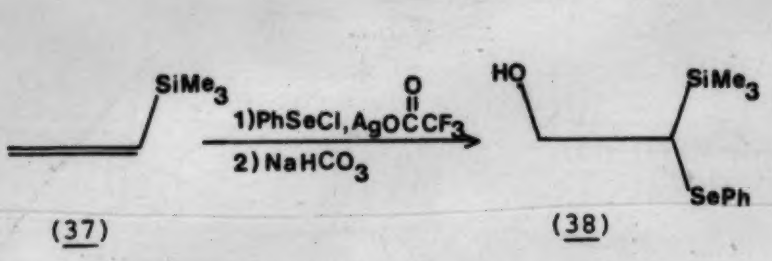
(30) (31) (32) (23)


SiMe$_3$
SePh
(32)
<O>
SiMe$_3$
SePh
O
(33)
fragm.
1) Sila-Pummerer
2) H$_2$O
SiMe$_3$
(35)
<O>
O
(34)
SiMe$_3$
(36)

(24)

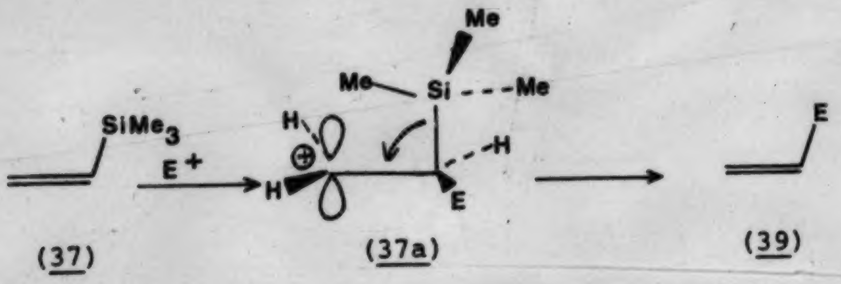
DISCUSSION

In order to test whether the discussed β-effect[45,47] of silicon could control the regiochemistry of addition of selenium electrophiles to unsaturated systems, we treated trimethylvinylsilane (37) with benzeneselenenyl trifluoroacetate [eq. (25)].


SiMe$_3$
1)PhSeCl,AgOC(O)CF$_3$
2)NaHCO$_3$
HO
SiMe$_3$
SePh
(37)
(38)

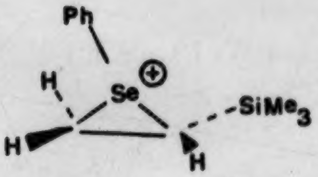
(81.7%) (25)

The production of the desired (38) as the only reaction product was quite remarkable,[49] since treatment of vinylsilanes with electrophiles almost always results in substitution of the trimethylsilyl group,[45] by the mechanism shown in eq. (26), where the silicon is probably assisted by a nucleophile in its elimination.

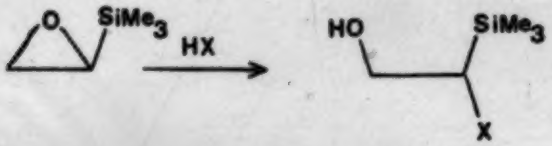

SiMe$_3$
E$^+$
Me
Me
Si
Me
H
⊕
H
H
E
E
(37)
(37a)
(39)

(26)

This equation illustrates a point of stereochemical significance, namely that the C-Si σ-bond responsible for stabilizing the positive charge (presumably[45a] through hyperconjugative effects) must lie in the same plane as the empty adjacent p orbital. So one can predict a minimum in the β-effect when the opposite arrangement (i.e., perpendicular) of the two orbitals is observed. Since no substitution takes place in our case, one can assume that there is hindrance to the attainment of the geometry (37a) and this might be due to bridging of the selenium with the β-carbon.[50] The observation that the trifluoroacetyl group binds to the β-carbon, however, suggests that the β-carbon bears some positive charge. If this were not the case and the opening of (40) were to be considered an S_N2 process, one might expect the opposite regiochemistry for the following reason: silicon is known to accelerate substantially an S_N2 process occurring at an α carbon atom,[51] and an illustrative example is given by epoxy-silanes which react, even in acid-catalyzed reactions, at the α-carbon[52] [eq. (26)].

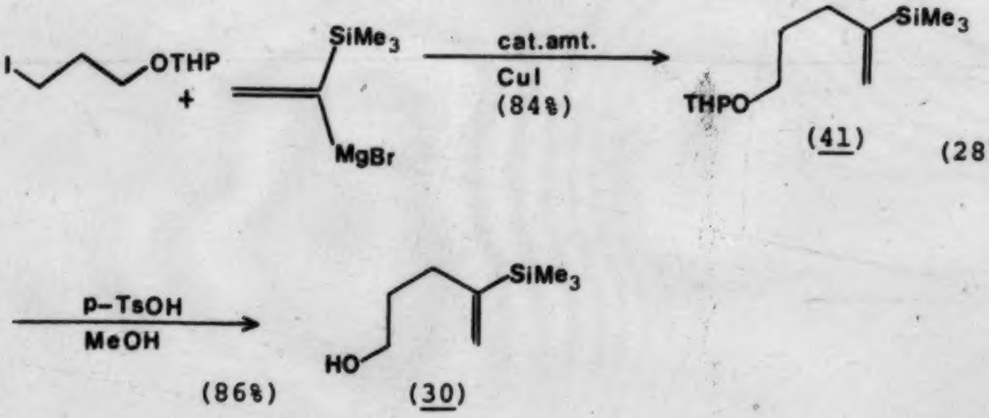


(40)


SiMe3
HX
HO
SiMe3
X

(27)

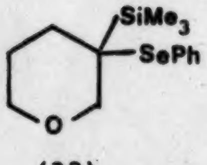
Encouraged by this result, we proceeded to test an intra-molecular case, for which any prediction was difficult, due to lack of precedent for such a process.[53] The required unsaturated alcohol (30) was readily available using the well known cuprous-ion catalyzed coupling between Grignard reagents and alkyl halides;[54] our starting material was obtained in two steps from known chemicals, as shown in eq. (28).


I
OTHP
+
SiMe3
MgBr
cat.amt.
CuI
(84%)
SiMe3
THPO
(41)
p-TsOH
MeOH
(86%)
SiMe3
HO
(30)

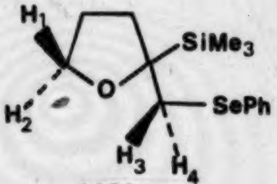
(28)

When we treated (30) with selenium electrophiles, however, we failed to obtain good yields of a cyclized product. The reaction with silver trifluoroacetate-benzeneselenenyl chloride was found to work best in THF as a solvent, but to produce only a low yield (28.8%) of cyclized product. By TLC there was substantial streaking of the reaction mixture and this, using our experience with the cyclization of unsaturated urethanes (described in part 1), was taken to mean that the initial benzeneselenenyl chloride-substrate adduct(s) constituted substantial part of the species in solution. Longer reaction times, the use of a base and also of silica gel, failed, however, to improve the yield. In the case of silica gel we employed conditions similar to the ones used with unsaturated urethanes, but this time we observed slow consumption of benzeneselenenyl chloride (presumably by decomposition of the initial adduct, since the reaction mixture was colorless or pale yellow) and the presence of starting material as the main component. It seems likely that the cyclization rate in this case is particularly slow, and reversion to starting material with hydrolysis of benzeneselenenyl chloride at the silica surface (eventually to diphenyl diselenide and benzeneseleninic acid) takes precedence.

We briefly examined other electrophiles as cyclizing agents (iodine, N-bromosuccinimide, iodonium di-*sym*-collidine perchlorate,[55] N-phenylselenophthalimide[9j]) without success. We did not continue our attempts mainly because it was clear that our cyclized product was the unwanted five-membered cyclic ether (*42*) and not the desired (*32*). The structure was assigned


SiMe3
SePh
O

(*32*)

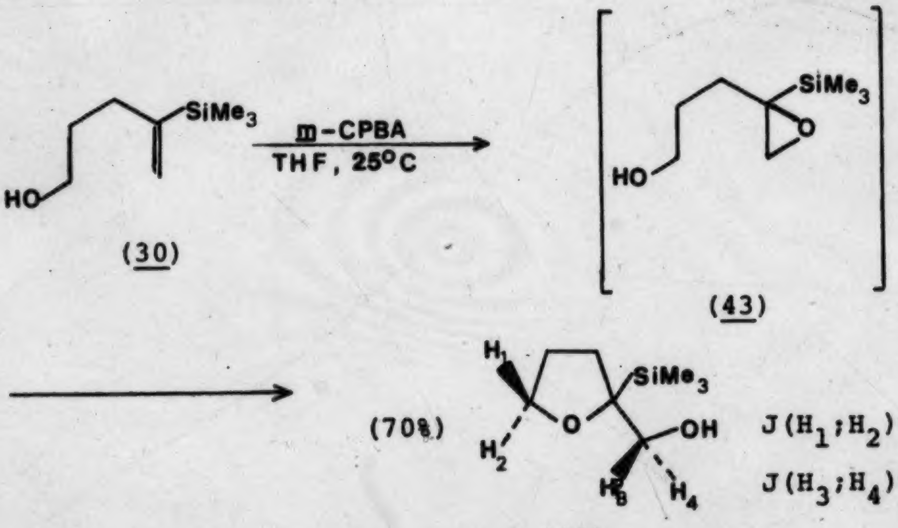

H1
SiMe3
O
H2
SePh
H3
H4

(*42*)

$J(H_1;H_2)$=8.2 Hz

$J(H_3;H_4)$=12 Hz

on the basis of the value of the geminal coupling constant for the protons α to the oxygen atom. This value (8.2 Hz), obtained by decoupling experiments, is typical of tetrahydrofurans. The value expected for (*32*) would be *ca*. 11.5 Hz.[56] To further support our assignment, when (*30*) was treated with *meta*-chloroperbenzoic acid, [eq. (29)]


SiMe3
HO
m-CPBA
THF, 25°C
SiMe3
O
HO
(70%)
H1
SiMe3
O
OH
H2
H3
H4

(*30*)

(*43*)

(29)

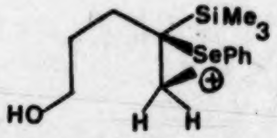
$J(H_1;H_2)$=8.4 Hz

$J(H_3;H_4)$=11.4 Hz

(*44*)

the primary alcohol (44) was obtained directly, without isolation of the intermediate epoxysilane (43), in good yield [both the readiness with which (43) is opened and the regiochemistry observed illustrate the α-effect discussed above]. The structure (44) was assigned on the basis of the ^{1}H-NMR spectrum in DMSO-d_6: in the spectrum, the hydroxylic proton appears as a clean triplet at δ 4.47 (J = 5.5 Hz).

The value of the coupling constant between the geminal hydrogen atoms α to the ether oxygen atom (8.4 Hz) is very close to the value given for (42), confirming in such a way our assignment. We are forced to conclude that the trimethylsilyl group cannot in this case exert an adequate β-effect on carbon because of the relative orientation of the C-Si and C-Se bonds in (31), which deviates from the parallel alignment necessary for the stabilization of a developing positive charge by the silicon.[57] This observation contrasts with the results obtained using the simple vinylsilane (37), in which, however, the observed regiochemistry of addition might have been the result of thermodynamic control.[58]



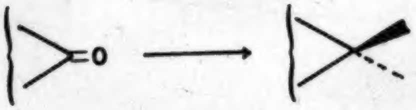
(31)

Presently it is not easy to predict the ease of equilibration (32) $\rightleftarrows$ (42) under the reaction conditions.[9d,h] The reason why ring closure of (30) proceeds so slowly and does not go to completion, is rather difficult to understand, especially if compared with the extremely facile process (43) → (44). It is, therefore, unlikely that the trimethylsilyl group exerts a significant steric effect. Further speculation is impossible in the absence of further data (for example, experiments on other functionalized vinylsilanes).

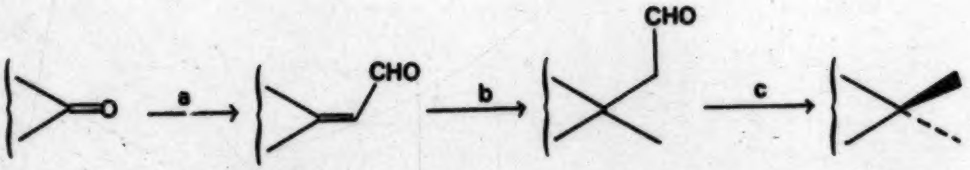
PART 3: ADDITIONS OF CUPRATES TO α,β-UNSATURATED ALDEHYDES.

INTRODUCTION

Geminal methyl groups attached to a carbon atom, especially as part of a carbocyclic system, are a common feature in many natural substances.[59] Due to the availability of the carbonyl group, its versatility for assembling molecular frameworks and its susceptibility to further transformations, we were led to explore the possibility of devising an efficient, reliable, stepwise method of converting a carbonyl function into a geminal dimethyl group,[60] as in eq. (30). A chemically reasonable scheme for this transformation is shown in eq. (31).



(30)



(31)

A similar scheme involving the intermediacy of α,β-unsaturated sulfones has been investigated by Posner.[60b] The introduction of the methyl group was achieved using lithium dimethylcuprate, but the yields were clearly not satisfactory. Our scheme, apart from step (a)[61] and step (c),[62] which are well precedented, presents the problem of a conjugate addition to α,β-unsaturated aldehydes. It is known that with organolithium reagents enals are more susceptible to 1,2-addition than enones.[63] Grignard reagents give usually 1,2-addition, although isolated cases of conjugate additions have been reported.[64] Organocadmium compounds[65] are also poor in respect to 1,4-additions. Enals can function as Michael acceptors,[66] although in some cases this can be the result of thermodynamic control.[66e] In general, there has been reluctance to use enals in conjugate additions, due to the unpredictability of the regiochemistry (i.e., 1,2 vs. 1,4) of the addition.[67]

Our obvious initial choice as reagent for step (b) was lithium dimethylcuprate. Cuprates undergo effective conjugate addition to enones[68] but only a few scattered reports exist in the literature where α,β-unsaturated aldehydes have been employed as substrates.[69] Recently, however, two detailed studies[70] on the subject have appeared: Lithium dimethylcuprate adds smoothly in a conjugate fashion to simple α,β-unsaturated aldehydes, but significant amounts of 1,2-addition (up to 64%[70a]) occur when more branched substrates are used. Other cuprates give variable amounts of 1,4-addition, and the trend seems to fit the scale proposed by House[71], which measures the relative ability of lithium dialkylcuprates to undergo conjugate addition with enones [eq. (32)].

n-butyl ~ vinyl > phenyl ~ methyl ~ *sec*-butyl
> *tert*-butyl ~ allyl (32)

House[72] has proposed that conjugate addition of cuprates to enones proceeds *via* initial electron transfer, and has correlated the reduction potential of several unsaturated compounds with their reactivity in conjugate additions with cuprates. The conclusion[71] is that the reduction potential of the unsaturated carbonyl compound should be within the range -1.3 to -2.3 V in order to obtain conjugate addition of lithium dimethylcuprate in good yield. House's mechanism is not universally accepted[74] but the correlation "reduction potential—reactivity in 1,4-addition" seems to allow predictions with most α,β-unsaturated compounds, particularly ketones and esters.[72]

In the case of enones the main competitive reaction is enolization,[75] while 1,2-addition is less often observed. In fact, saturated ketones do not react readily with cuprates to form 1,2-adducts.[76] For saturated aldehydes, however, the situation is different, reaction with lithium dimethylcuprate resulting in rapid (even at -90°C) 1,2-addition,[77] by an unknown mechanism. House[73] has given a set of empirical rules to estimate the reduction potential of α,β-unsaturated carbonyl compounds. Most of the enals studied recently by Normant[70] have a reduction potential well within the range useful for conjugate addition, but nevertheless much 1,2-addition is sometimes observed.

It is clear that α,β-unsaturated aldehydes are a special case within the group of substrates for cuprate conjugate additions, due to their tendency to react in the 1,2 mode. We reasoned that, if conjugate addition occurs via electron transfer and 1,2 addition, in principle, via a different mechanism,[78] the use of cuprates with a more negative reduction potential might selectively enhance the rate of 1,4-addition, possibly without noticeable effect on the rate of 1,2-addition. Since determinations of oxidation potentials of cuprates by electrochemical measurements are precluded by the slow rate of electron transfer from the cuprate to the electrode surface,[79] we decided to investigate empirically a series of cuprates capable, in principle, of delivering a methyl group to enals, in order to seek selectivities better than those observed in the case of lithium dimethylcuprate.[70]

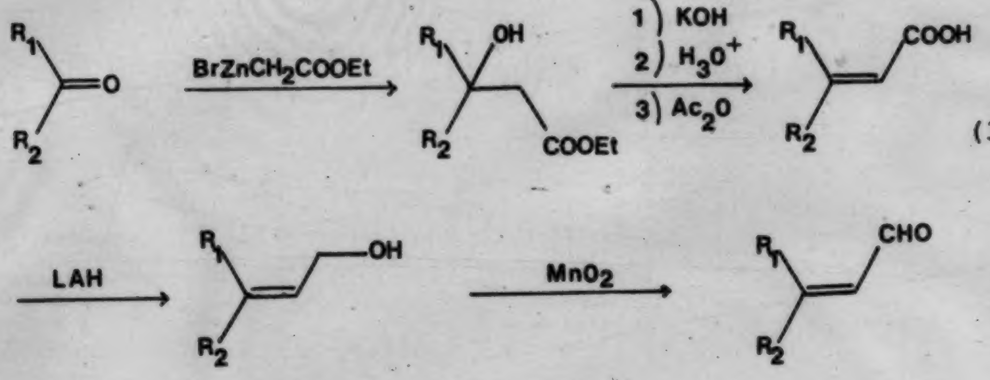
We also planned to test a few of the literature methods available to perform step (a) in eq. (31), and to carry out some decarbonylations using Wilkinson's reagent, tris-triphenylphosphine rhodium(I) chloride[80] in order to establish whether the quarternary center adjacent to the reaction site has a significant effect on the rate of decarbonylation.

DISCUSSION

(A): Availability of α,β-unsaturated aldehydes.

Of the many possible syntheses of α,β-unsaturated aldehydes, we took into consideration only the ones that use as a substrate a ketone (or an aldehyde) and that proceed with a two-carbon homologation to an enal,[61] as in our original plan [eq. (31)]. The preparation of our substrates serves to illustrate some of the many methods available for such a transformation.

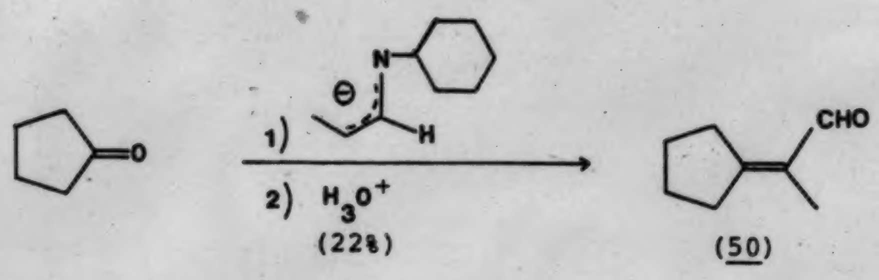
Ketones undergo the well-known Reformatsky reaction[81] and the resulting hydroxy esters can be converted ultimately into enals, as shown in eq. (33).



(33)

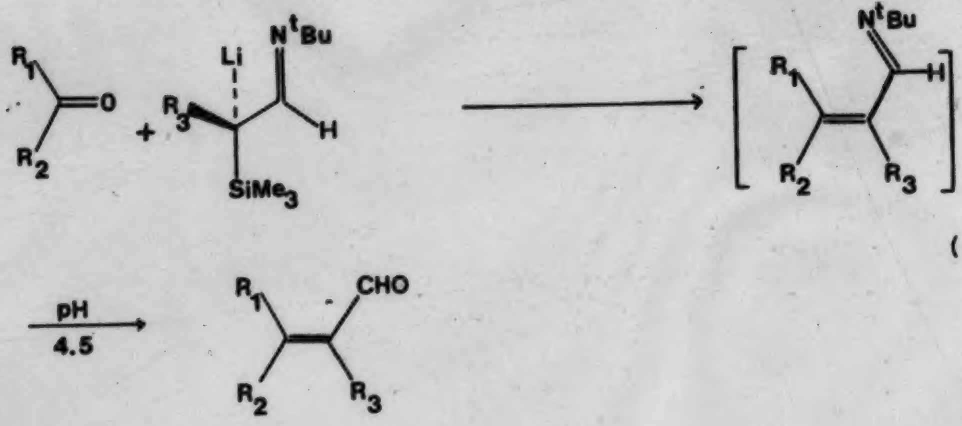
Thus, enals (45)[61e] and (48)[82] (p. 54) were obtained by MnO_2

oxidation of the parent allylic alcohols. This scheme certainly does not appear to be advantageous, due to the fact that several steps are involved. A modification of the above idea involves the use of a directed aldol condensation,[61m] which is a much more direct approach [eq. (34)].



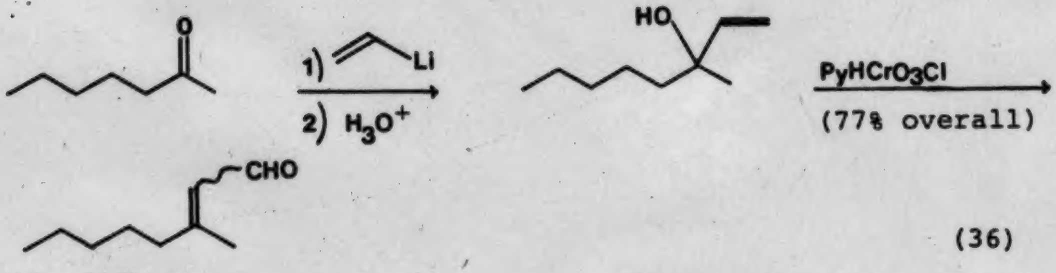
(34)

As illustrated by the preparation of (50),[70a] the method involves essentially one step, but the harsh conditions required in the dehydration of the intermediate β-hydroxy aldehyde - a much more sensitive substrate than a β-hydroxy ester - lower the yields significantly. An efficient way of avoiding such a step is to use anions from α-trimethylsilyl t-butylimines.[61f] This method [eq. (35)] is operationally simple, and we tested it in the preparation of (45), (49) and (52) (p. 54-55). We found that, although the yields were uniformly acceptable, the reaction mixture always contained small amounts (typically 10-20%) of unreacted saturated ketone, and its presence could not be avoided by altering the concentrations of



(35)

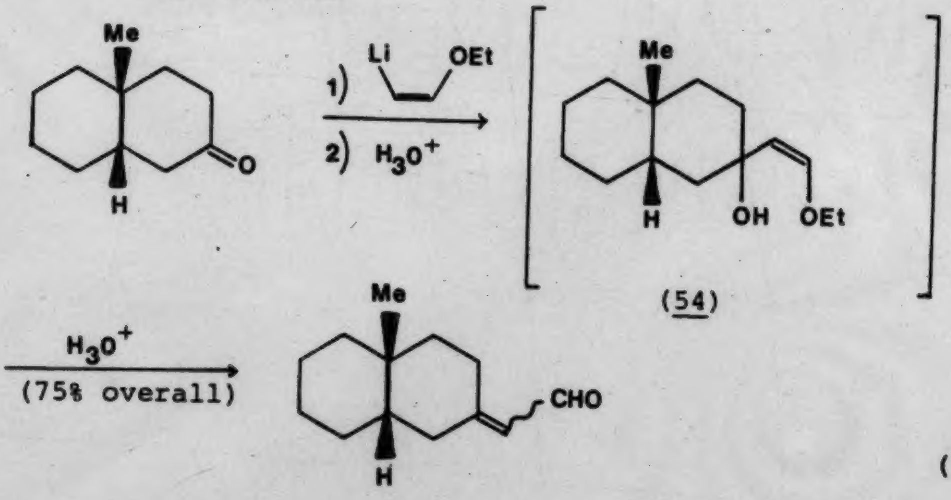
the species in solutions (i.e., using an excess of imine anion). On the rather small scale that we employed, this implied a careful purification by flash chromatography,[39] and this technique was always accompanied by loss of product in mixed fractions; consequently our yields were usually not higher than 50%. It is likely that, operating on a larger scale and purifying the product by distillation, one might obtain better isolated yields. Another method[61g] which is relatively convenient but presents, too, the disadvantage of affording a product accompanied by starting material, is illustrated by the preparation of (46) [eq. (36)].


1)
Li
2) H_3O^+
HO
PyHCrO3Cl
(77% overall)
CHO

(46)

(36)

Finally, the most convenient method, in our experience, was used in the synthesis of (51) and (53) (p. 55) and is shown in eq. (37).[61t]


Me
H
O
1) Li OEt
2) H_3O^+
Me
H
OH
OEt
H_3O^+
(75% overall)
Me
H
CHO

(54)

(53)

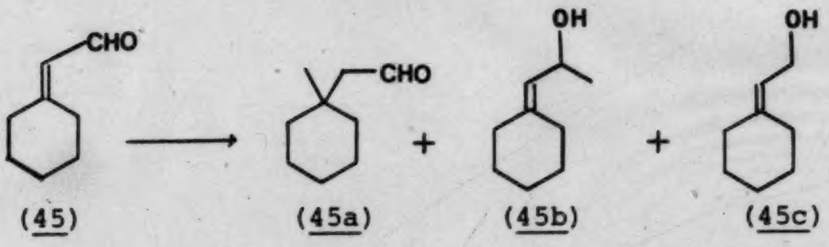
(37)

The method exploits the rapid [1,3] transposition of tertiary allylic alcohols, and in this case the resulting carbinol (54) is rapidly hydrolyzed under mildly acidic conditions. With this one-step procedure little starting ketone is observed, the purification of the product is simple and the yields are high. We tested the method also in the preparation of (45) (p. 54) and we obtained a 90% isolated yield.[61r] The required Z-1-lithio-2-ethoxyethylene can be prepared either from Z-1-bromo-2-ethoxyethylene by Br/Li exchange,[61t] or from (2-ethoxyvinyl)-tri-n-butylstannane by Sn/Li exchange.[61r,s] Since the bromide is easier to prepare[61t] and is now also commercially available (Aldrich), its use is certainly more convenient.

Other methods[61] are available for the synthesis of α,β-unsaturated aldehydes, and we believe that this class of compounds has become now sufficiently accessible to warrant its use in organic synthesis. Our experience shows that these compounds are rather unstable however, and, if kept at room temperature in ordinary, stoppered, vials, they undergo appreciable decomposition after 24 h. They can be stored without evidence of decomposition under a nitrogen atmosphere at -20°C for short periods (2-4 weeks), so that their use in synthesis should not pose any special problems.

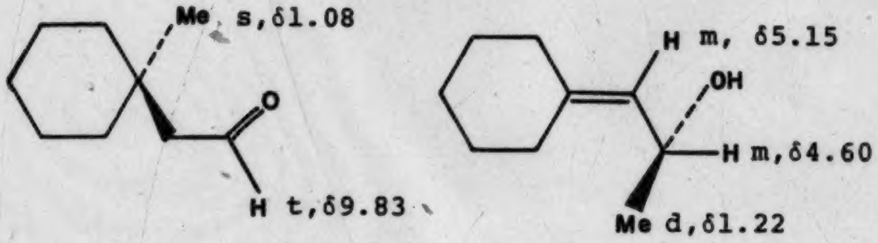
(B): Cuprate additions to α,β-unsaturated aldehydes.

Our model compound for the conjugate addition of cuprates was enal (45), which possesses an exocyclic double bond. This compound was chosen due to the large number of natural substances[59] featuring a gem-dimethyl group attached to a six-membered carbocyclic skeleton.



(38)

When we treated our substrate with a slight excess of lithium dimethylcuprate in ether at -75°C to -40°C and quenched the solution with a saturated ammonium chloride solution, we obtained a 71% yield (corrected for recovery of 9% starting material) of a mixture of (45a) and (45b) in the ratio 87:13. We found it especially convenient to measure this ratio by ^{1}H-NMR, by integration of the signal due to the aldehydic hydrogen for (45a) (triplet at δ 9.83) and the signals due to the olefinic hydrogen or to the hydrogen attached to the carbon bearing the hydroxyl (multiplets at δ 5.15 and 4.60, respectively) for (45b). Alternatively, integration of the signals due to the methyl groups in (45a) and (45b) was also used. These latter signals are fairly well separated. The diagnostically significant signals are summarized in Scheme 2.



Scheme 2

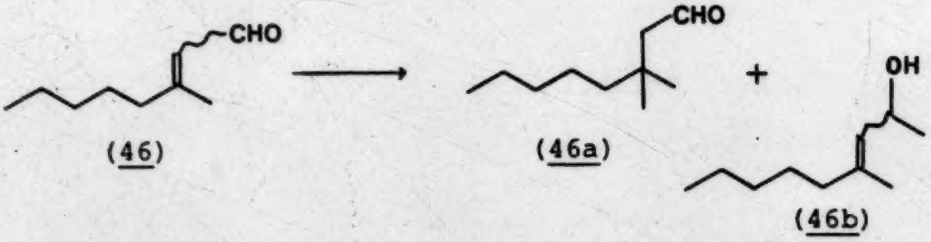
We also prepared an authentic sample of the 1,2-adduct by reaction of (45) with methyllithium in ether, and, by comparison of VPC and NMR data, we could confirm that the minor product in the lithium dimethylcuprate run was indeed the 1,2-adduct. The ratio 87:13 agrees qualitatively with the ratios obtained by Normant[70a] for aldehydes with a similar substitution pattern. It must be noted that the approximate reduction potential of (45), on the basis of House's[73] parameters, is -2.1 V, a value that is within the range for which conjugate addition is predicted without complications. As noted in the introduction, it is likely that this range is narrower in the case of enals, and we sought a more selective reagent for the conjugate addition. It was noted recently by Ashby[83] that when one adds an ethereal methyllithium solution (dissolved lithium salts do not seem to have any influence) to a slurry of purified[84] cuprous iodide in ether, one obtains a yellow-orange suspension of methyl copper. The mixture then slowly decolorizes on further addition of methyllithium and the precipitate starts to dissolve. A clear colorless solution is obtained when 1.67 equivalents of methyllithium have been added, that is, before the stoichiometry of lithium dimethylcuprate has been reached. Thus, there must be a complex in solution corresponding to a stoichiometry $Me_5Cu_3Li_2$ which is formed prior to the formation of the better known Me_2CuLi. Ashby[83] could not characterize the species by NMR, but by analogy with his observations in dimethyl ether, where the initially formed complex Me_3Cu_2Li could be detected clearly, he postulated that 2:3 is the lowest ratio of Li:Cu that can be obtained in a methylcuprate in ether. In retrospect, it is very surprising that after so many years of cuprate chemistry[68] none of the many chemists who have prepared solutions of lithium dimethylcuprate seem ever to have reported this observation. Certainly, to our knowledge, none has acted upon it.

This state of affairs can, in part, be due to the fact that $Me_5Cu_3Li_2$ and Me_2CuLi behave very similarly in the conjugate addition to enones[85] and, moreover, the complex Me_3CuLi_2,[83] which is formed on further addition of MeLi to lithium dimethylcuprate solutions, is also a good carrier of the methyl group in conjugate additions to enones.[85] Thus, a deficiency or an excess of methyllithium in the preparation of lithium dimethylcuprate does not affect its reactivity (reaction rates are, however, slightly different[85]) with enones, and this has probably prevented - through the observation of some abnormal product distribution - the discovery of the reagent Me_5Cu_3Li. We repeated Ashby's procedure[83] using freshly titrated methyllithium containing 5% lithium chloride, and we indeed observed that a clear colorless solution is obtained at 0°C when 1.67 equivalents of methyllithium have been added. Addition of 2 equivalents[86] of our enal (45) to this solution, in the temperature range -75°C to -40°C, followed by work-up, gave (45a) and (45b) in the ratio of 99:1, plus another compound that was identified as (45c) upon comparison (VPC, NMR) with the data obtained on an authentic sample. Typically (45c) comprises 3-7% of the total product, as judged by VPC relative peak areas. There is precedent in the literature for reductions of aldehydes during lithium dimethylcuprate reactions,[87] presumably by methylcopper, and to confirm this we ran a reaction using methylcopper as a reagent: consumption of the enal was rather slow even at -10°C, and (45a) plus (45c) were obtained in a 2:1 ratio (by VPC), with no trace (<0.5%) of (45b).

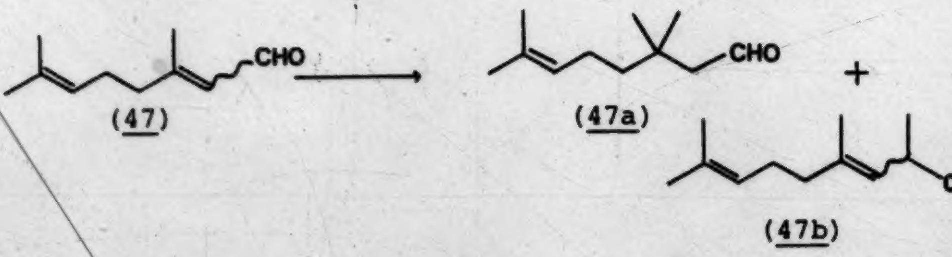
We did not investigate further this reductive side-reaction since we found that, by using the cuprate and the enal in a 1:1 ratio, reduction could be suppressed completely.

A further point deserves comment in this reaction: the quenching procedure, as recognized by Normant,[70a] is more critical here than in the case of enones; in fact, aldehydes can undergo rapid self-condensation or other side reactions (Cannizzaro) during quenching. These processes are initiated by the strong bases that are present before the quenching is complete. Indeed, our yield was 71% when we poured onto the reaction mixture at 0°C a cold ammonium chloride solution, but when we quickly added an excess of neat acetic acid at -75°C, followed by work-up and distillation, (45a) could be obtained in 90% yield, and the material contained only traces (1%) of its isomer (45b), the 1,2-adduct.

Our conclusion was that $Me_5Cu_3Li_2$ does indeed behave differently from Me_2CuLi in ether, at least in its reaction with α,β-unsaturated aldehydes, and its use might allow us to effect the process (b) in our original plan [eq. (31), page 38] with high chemical yield and excellent regioselectivity. We decided, therefore, to study the properties of this new cuprate reagent in further detail, especially with respect to its reaction with α,β-unsaturated aldehydes. We studied the regiochemistry of the addition of $Me_5Cu_3Li_2$ to a number of representative enals (calculated[73] reduction potentials: -2.1 to -2.2 V), and compared our results with the ones obtained similarly with Me_2CuLi. The presence of 1,2-adducts was confirmed (or excluded) in each case by comparison of the VPC and NMR of the total reaction product with the data obtained from authentic 1,2-adducts, prepared by reaction of MeLi with the enals. Our comparative study is summarized in Table 3 (page 54). Enals (46) and (47) illustrate the use of acyclic β,β-disubstituted

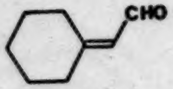
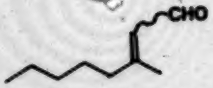
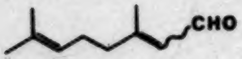
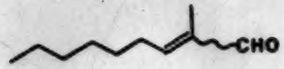


(39)



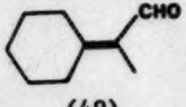
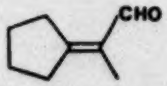
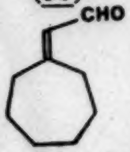
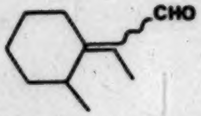
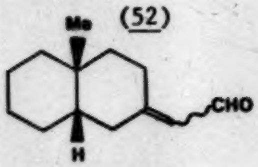
(40)

Table 3. REACTIONS OF VARIOUS ENALS WITH $Me_5Cu_3Li_2$ AND Me_2CuLi.

Starting Material	Reaction Solvent; T/°C[a] (quench)	Reagent	% Yield[b]	% 1,4-Methylation[c]	% 1,2-Methylation[c]
 (45)	Et_2O; -40 (ACOH)	$Me_5Cu_3Li_2$ Me_2CuLi	90 71[d]	99.0 87.0	1.0[e] 13.0
 (46)	Et_2O; -40 (ACOH)	$Me_5Cu_3Li_2$ Me_2CuLi	90 90	>99.5 91.5	<0.5[f] 8.5
 (47)	Et_2O; 0 (ACOH)	$Me_5Cu_3Li_2$ Me_2CuLi	80 78	>99.5 90.0	<0.5[f] 10.0
 (48)	Et_2O; -20 (Me_3SiCl)	$Me_5Cu_3Li_2$ Me_2CuLi	92 92	98.5 94.5	1.5 5.5

continued...

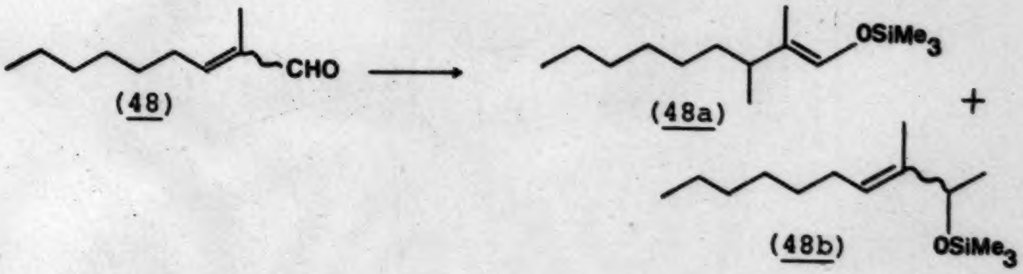
Table 3. (continued)

 (49)	Et_2O-pentane; 0 (Me_3SiCl)	$Me_5Cu_3Li_2$ Me_2CuLi	88 91	>99.5 80.0	<0.5[f] 20.0
 (50)	Et_2O; 0 (Me_3SiCl)	$Me_5Cu_3Li_2$ Me_2CuLi	85 86[g]	77.5 36[g]	22.5 64[g]
	Et_2O-pentane; 0 (Me_3SiCl)	$Me_5Cu_3Li_2$	88	85.0	15.0
 (51)	Et_2O; -20 (ACOH)	$Me_5Cu_3Li_2$ Me_2CuLi	88 88	94.5 83.0	5.5 17.0
 (52)	Et_2O-pentane; 0 (Me_3SiCl)	$Me_5Cu_3Li_2$ Me_2CuLi	88 87	46.0 48.5	54.0 51.5
 (53)	Et_2O; -20 (ACOH)	$Me_5Cu_3Li_2$ Me_2CuLi	86 84	98.0 97.5	2.0 2.5

---

[a] Temperature refers to the highest temperature reached by the reaction mixture before the reaction was quenched (at -75°C). [b] Yields refer to isolated and distilled materials of >97% purity (VPC). [c] Ratios determined by 200 MHz NMR, except where indicated. [d] The mixture was quenched with a saturated aqueous ammonium chloride solution. [e] Ratio determined by VPC. [f] Actually, none was detected (VPC, NMR). [g] Data from Ref. 70a.

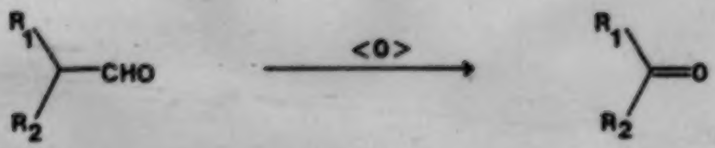
substrates. Both enals gave essentially only 1,4-addition with $Me_5Cu_3Li_2$, while Me_2CuLi gave some 1,2-addition (8.5% and 10%, respectively).* The reaction of citral with Me_2CuLi has been studied already: Normant[70a] reports a 19% 1,2-addition, while other authors report only ca. 5%[69j] (estimated by VPC relative peak areas). Operating at lower temperatures than Normant, we find less 1,2-addition, not surprisingly. Our figures, obtained by NMR, were confirmed by separation and isolation of the two adducts (see experimental). The case of (48) illustrates the use of α,β-disubstituted enals. We found little (1.5%) 1,2-addition with $Me_5Cu_3Li_2$, although Me_2CuLi also gave mainly (94.5%) 1,4-addition. We found that in the case of α substituted enals, the aldehydes resulting from conjugate additions were unstable in the reaction mixture, decomposing to give mainly saturated ketones with one less carbon atom [eq. (42)].



(41)

---

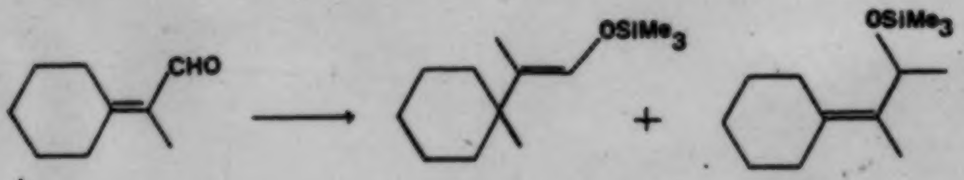
*These and similar following figures refer to relative proportion of the specific adduct in the total distillate (see Table 3).



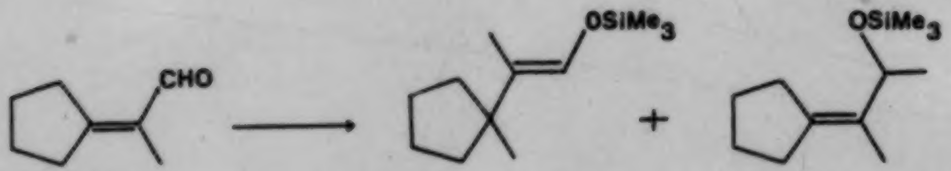
(42)

This reaction was first observed by Normant[70] in his ammonium chloride-quenched reactions, and we found that acetic acid as a quenching agent does not prevent this oxidative decarbonylation. The mechanism of the reaction is not known, but cuprous or cupric ions almost certainly play a role.[88] Following Normant,[70a] we have quenched our reactions at -75°C with chlorotrimethylsilane - triethylamine - HMPA,[89] and isolated the trimethylsilyl enol ethers of the aldehydes in good yields. These derivatives were also suitable for complete characterization, including elemental analysis. Normant[70b] has shown that, if desired, the parent aldehydes can be recovered efficiently by fluoride ion-catalyzed methanolysis of the enol ethers. Enals (49) and (50) were chosen with the purpose of testing our reagent with less easily reduced substrates [estimated[73] reduction potential is -2.2 V for both (49) and (50)].

Compound (50) contains a double bond exocyclic to a 5-membered ring, while in (49) the double bond is exocyclic to a 6-membered ring, and this introduces a strain,[90] possibly making the substrate more prone to



(49) (49a) (49b) (43)



(50) (50a) (50b) (44)

conjugate addition.

Compound (50) had been tried already by Normant[70a] as a substrate for Me_2CuLi reactions, and from his results (64% 1,2-addition) we knew it to be a particularly difficult case.

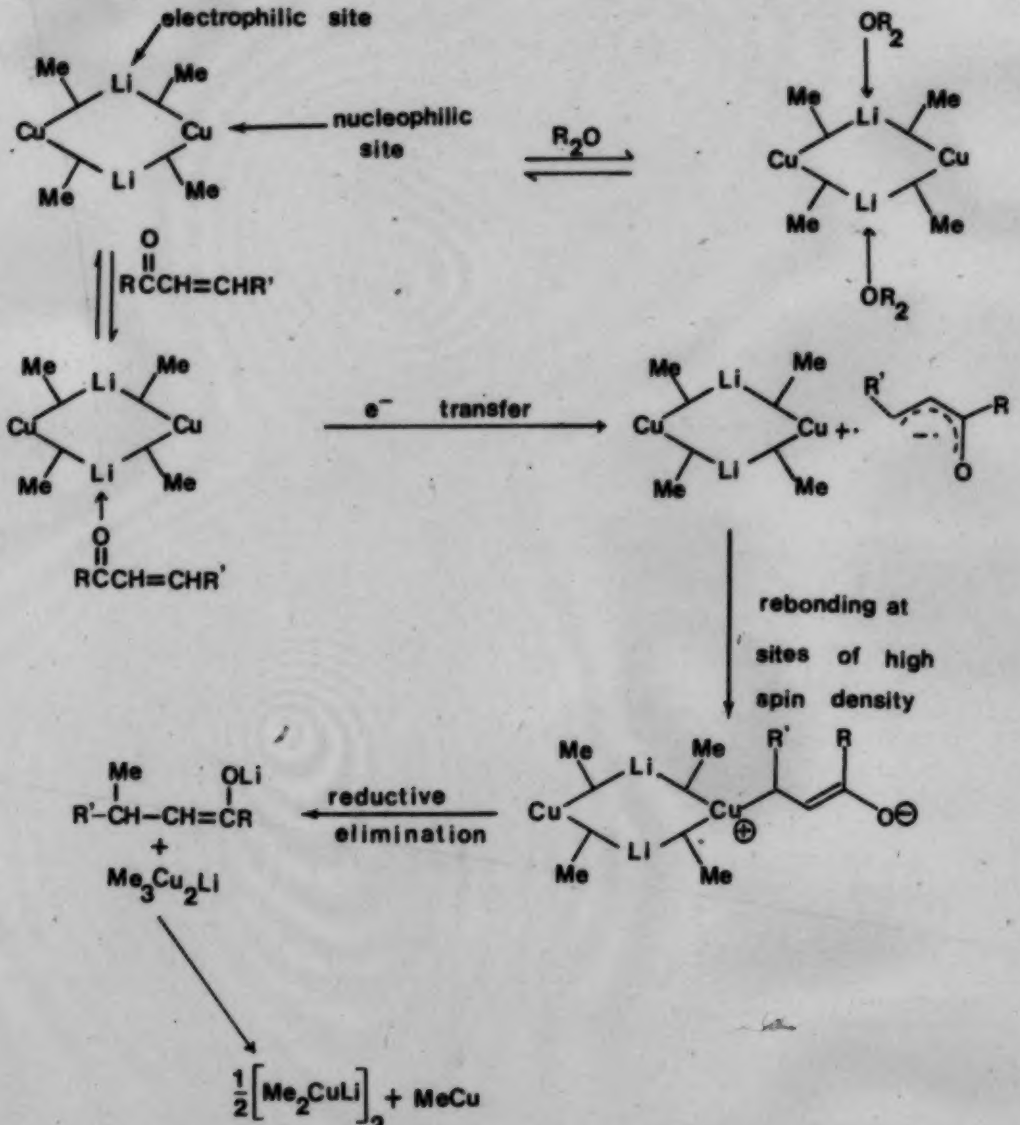
$Me_5Cu_3Li_2$ in ether gave 77.5% conjugate addition, a substantial improvement over the 36% obtained with Me_2CuLi. Following the observation by House[71] that the introduction of a non-polar solvent promotes 1,4-addition relative to side reactions (enolization, in the case of enones) that are not related to the electron transfer process, and that this effect is quite appreciable for substrates having reduction potentials at the threshold value for useful conjugate additions (-2.3 V for enones, possibly -2.2 V for enals), we tried a mixture of ether-pentane as reaction solvent in our $Me_5Cu_3Li_2$ runs on (50). It was, of course, not clear a priori whether the introduction of another solvent would alter the nature of our "ate" species. We indeed observed no visible change (i.e., coloration or precipitation) upon addition of three volumes of pentane to an ether solution of $Me_5Cu_3Li_2$, and, by addition of (50) to this solution, we could isolate an 85:15 mixture of (50a) and (50b) in good yield. Therefore, the use of pentane does indeed represent an improvement, in this case, with respect to using simply diethyl ether.

The case of (49) was even more fortunate: the use of an ether-pentane mixed solvent suppressed completely the 1,2-addition process, and (49a) was isolated pure as the only product in good yield. Me_2CuLi, even though ether-pentane was used as a solvent, still gave 20% of the 1,2-adduct (49b), identical with the material prepared by using methyllithium as nucleophile. When we repeated the run of (45) with Me_2CuLi in ether-pentane, however, we did not record any improvement over the 87:13 ratio of 1,4 vs. 1,2 addition, showing that pentane as co-solvent is only useful in limiting cases when the reduction potential of the enal is presumably around -2.2 V.

The role of the solvent in these conjugate additions has been discussed by House;[71] the cuprate cluster[91] presents electrophilic and nucleophilic sites, as shown in Scheme 3 (page 61). The electrophilic (Li) sites are very important because they complex with the carbonyl oxygen in the first stage of the process; consequently their complexation by solvent molecules slows down the initial cuprate-substrate equilibrium, and as a result of this, the whole process. In fact stronger donors, as DME or THF, have a deleterious effect on the conjugate addition process.

Since we had found a substrate, (50), in which even with $Me_5Cu_3Li_2$ a measurable proportion of 1,2-addition was recorded, we decided that (50) was the ideal system on which to test other cuprate reagents, in order to check whether we could find an even more selective species for the conjugate methylation. Still[76d] has proposed that Me_3CuLi_2 in ether is an efficient reagent for conjugate addition to unsaturated aldehydes but, since the species is in equilibrium with MeLi,[83] we doubted very much that the reagent could undergo conjugate addition in an efficient manner with enals. Indeed, when reacted with our substrate (50), the reagent gave mainly (96%) 1,2-addition. A species that deserved more serious consideration was the bromomagnesium analogue of our pentamethyl species. Recently Leyendecker[92] has introduced

Scheme 3


electrophilic site
nucleophilic site
Li
Cu
Me
R_2O
OR_2
RC(=O)CH=CHR'
e^- transfer
R'
R
O
rebonding at sites of high spin density
reductive elimination
R'-CH(Me)-CH=C(OLi)R
+
Me_3Cu_2Li
$\frac{1}{2}[Me_2CuLi]_2$ + MeCu

the reagents $MeR_4Cu_3(MgBr)_2$ as highly reactive cuprates, i.e., species that add in a conjugate fashion to enones that are difficult to reduce. We prepared a suspension of "$Me_5Cu_3(MgBr)_2$" according to the directions of the French authors, and added our enal (50) at -40°C. The result, somewhat surprising, was almost complete 1,2-addition (96%, vs. 4% 1,4-addition).

Another species meriting examination was the cuprate Me_3Cu_2Li, that has been characterized by Ashby[83] in THF and dimethylether. It had been recognized[71] that THF is not the ideal solvent for cuprate conjugate additions;[68] indeed once again 1,2-addition was the predominant process (80%, vs. 20% conjugate addition). Other products were detected by VPC and NMR, so that the addition process in THF is also inefficient with respect to the yield. Recently, after the completion of this work, Normant has proposed $Me_2CuMgCl$ in THF as a reagent for conjugate additions to enals. He has reported only one example, which is characterized by a rather low yield (49%).[70b]

Our results on the comparative study of the action of several cuprates on enal (50) are summarized in Table 4 (p. 63). It seems clear that $Me_5Cu_3Li_2$ in ether-pentane is by far the most promising reagent among those we have tried, and we went on with our study of its

Table 4. ACTION OF VARIOUS CUPRATES ON 2-CYCLOPENTYLIDENE-PROPIONALDEHYDE.

Conditions	% Yield[a]	% 1,4-Addn.[b]	% 1,2-Addn.[b]
Me_2CuLi, ether, 0°C[c]	86	36	64
$Me_5Cu_3Li_2$, ether -50°C ÷ 0°C	85.5	77.5	22.5
$Me_5Cu_3Li_2$, ether-pentane -50°C ÷ 0°C	88	85	15
Me_3CuLi_2, ether -50°C ÷ 0°C	84.8	4	96
$Me_5Cu_3Mg_2Br_2$, ether -40°C ÷ 0°C	92.0	4	96
Me_3Cu_2Li, THF -50°C ÷ 0°C	-[d]	20	80

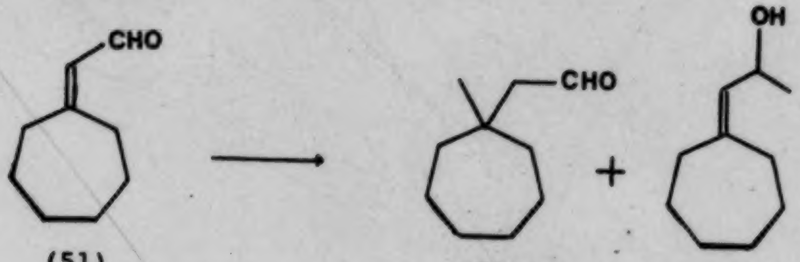
[a] Yields refer to distilled samples that were better than 99% pure (VPC, DEGS, 100°C) unless otherwise stated.

[b] Reactions were quenched with chlorotrimethylsilane (see Experimental part). Proportions of 1,4- and 1,2-adducts were estimated by ^1H NMR ($CDCl_3$, 200 MHz).

[c] Data from Normant, Ref. 70a.

[d] The mixture of (50a) and (50b) was contaminated by impurities (*ca.* 50% of the total product, estimated by VPC relative peak areas).

reaction with other α,β-unsaturated aldehydes.

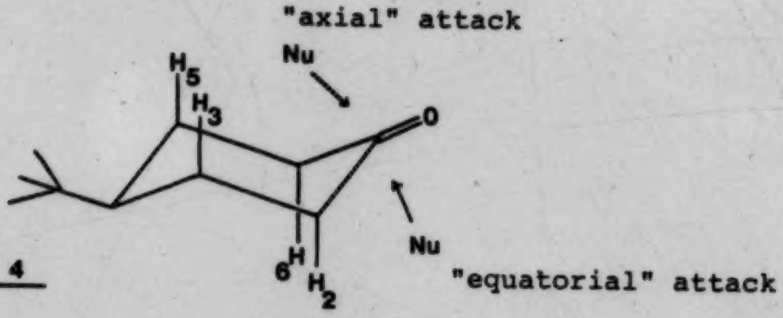


(51) (51a) (51b) (45)

The results with enal (51) are not easy to rationalize, since a fair amount (5.5%) of 1,2-addition was recorded even with $Me_5Cu_3Li_2$. (Me_2CuLi gave 17% of 1,2-adduct). The use of ether-pentane as a reaction solvent did not improve the result substantially.[93]

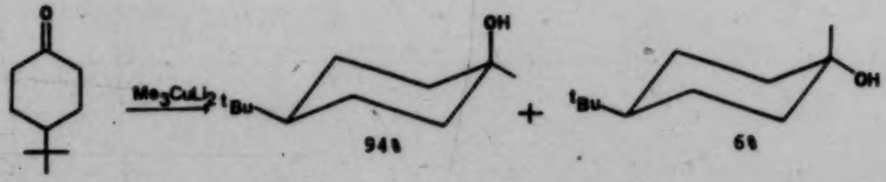
Finally, enals (52) and (53) (p. 55) were chosen in order to study the effect of remote substituents on the reaction course. The degree of double bond substitution influences directly the reaction course by controlling the reduction potential of the enal, while more remote substituents are expected to exert mainly steric effects. There is precedent for steric effects in cuprate conjugate additions[68] and it is known that lithium dimethylcuprate is a bulky species. We wanted to test in a qualitative way how our reagent would respond to situations in which approach to the conjugate double bond was hindered, in order to determine its steric requirements.

Work on addition of organometallic compounds to cyclic ketones has identified several stereoelectronic factors in controlling the preferential direction of approach by the incoming alkylating agent[94] (Scheme 4).


"axial" attack
Nu
H5
H3
O
Nu
H
6
H2
"equatorial" attack

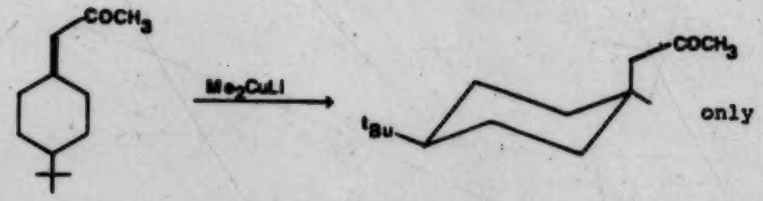
Scheme 4

It has been proposed[95] that in cyclohexanones the nucleophile is subject to (i) steric strain with the 3,5-axial substituents when attacking from an "axial" direction; (ii) torsional strain with the 2,6-axial substituents when attack is "equatorial". The two effects oppose each other, one favoring "equatorial" attack, the other promoting "axial" attack. For bulky nucleophiles (other than hydrides), "equatorial" attack is observed preferentially, with a variable degree of selectivity.


O
Me3CuLi2
tBu
OH
94%
+
tBu
OH
6%

(46)

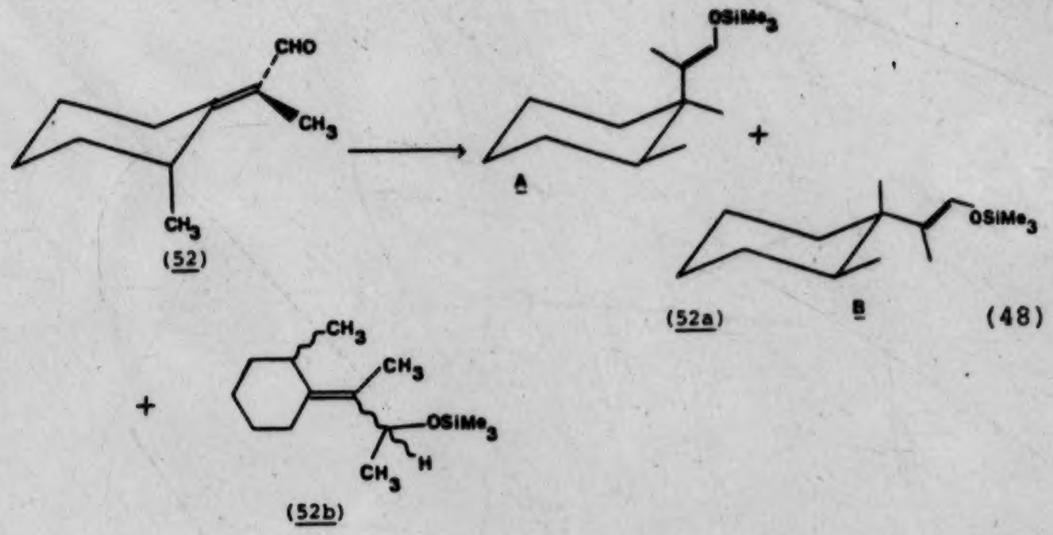
Using a reactive cuprate, Still[76d] observed excellent selectivity, on t-butylcyclohexanone, toward "equatorial" attack [eq. (46)]. Admittedly, the situation is different with α,β-unsaturated carbonyls, but a few examples[76a] suggest that the qualitative behavior is similar, "equatorial" attack being largely preferred. [see eq. (47)].



(47)

In the case of (52) (p. 67), we investigated the influence of one substituent α to the exocyclic methylene group in order to see whether it would exert any influence. Quite surprisingly, even in ether-pentane, we observed large amounts of 1,2-addition (54% vs. 46% 1,4-addition), $Me_5Cu_3Li_2$ being even less effective, in this case, than Me_2CuLi (51.5% 1,2 vs. 48.5% 1,4).

The 1,4-addition product was obtained in both cases as a 3:1 mixture of diastereoisomers. It is assumed, by analogy with the reaction of (49) (p. 55), where only one olefinic isomer (presumably E) of the trimethylsilyl enal ether was obtained in the conjugate addition, that here too we obtain two diastereomeric, isomerically pure E olefins.

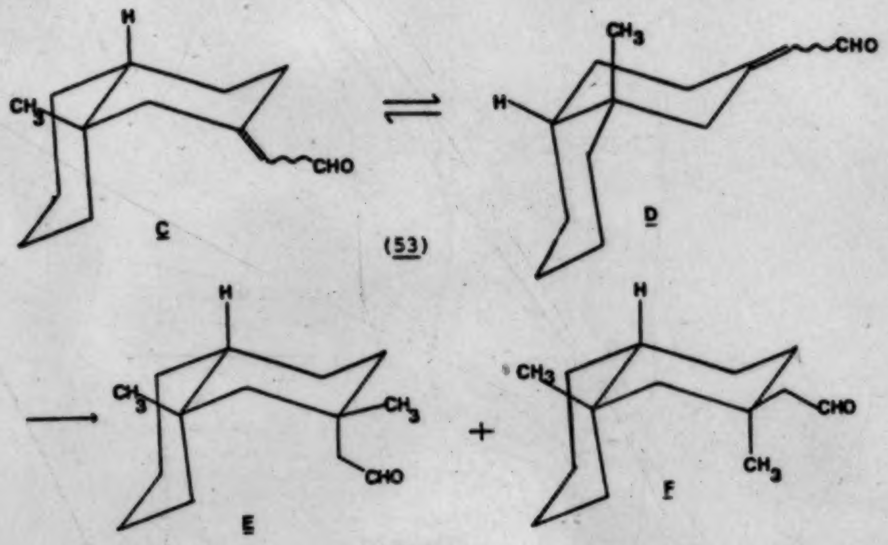


(52) A (52a) B (48)

(52b)

It was not possible to ascertain which diastereoisomer was formed preferentially; tentatively, we assign the structure A to the major isomer (methyl at C-1 shows a singlet at δ 0.90) while B, the minor isomer, shows the resonance due to the methyl at C-1 shifted downfield (singlet at δ 1.17), due to its axial position.[96] The assignment of the relative proportions would not, however, clarify completely the situation; in fact, it is not known, *a priori*, in which conformation (52) will react, so it is not possible to ascertain which isomer is the result of an "equatorial" attack and which is the result of an "axial" attack. We have drawn (52) arbitrarily with the methyl group in the axial position. Probably, due to A (1,3) strain[97] the methyl group is indeed present largely in the axial position, as shown, but it is not known in which conformation (52) will react preferentially. If we extend the considerations made in the case of cyclohexanones to our present situation, the adverse effect on the conjugate reaction can be explained by invoking an interaction between the nucleophile and the axial methyl group, so that "axial" attack would become predominant, to form A, and the overall reaction would be hindered, since the "axial" attack is a disfavored path, not normally observed.[76a] If the reacting species has an equatorial methyl group, it seems harder to rationalize the pronounced deleterious effect of the substituent.

Although it is not easy to reach a definite conclusion on the basis of this single example, it is clear that, when alkyl substituents are introduced in the 6-membered ring in the position α to the exocyclic double bond of the enal, the reaction with $Me_5Cu_3Li_2$ loses much of its selectivity, due to steric and/or torsional strain factors. It would seem, on the basis of this discussion, that substituents at the β and γ positions should not have much



(53)

(53a)

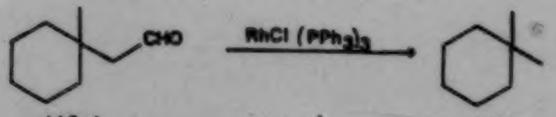
(49)

effect on the course of the conjugate addition, which should then proceed by its usual "equatorial" approach. The results with (53) suggest that this is the case (98:2 1,4 vs. 1,2 addition with $Me_5Cu_3Li_2$), although in this case once again we could not assign the structure of the two diastereomeric aldehydes by inspection of their spectral properties. By VPC, their ratio was 95:5. Owing to the conformational mobility of (53), equatorial attack can occur on both conformers C and D, to yield the two diastereoisomers E and F, and it is not easy to predict *a priori* which path is more favorable. In this reaction, remarkably, Me_2CuLi shows essentially the same results as $Me_5Cu_3Li_2$, little (2.5%) 1,2-addition being observed. This experiment concludes our efforts with respect to the reaction of α,β-unsaturated aldehydes with cuprates.

It seems to us that the use of enals as conjugate addition substrates can be very useful in synthesis, despite the fact that they have been little used, so far, in this respect. The species $Me_5Cu_3Li_2$ undergoes conjugate addition to enals having partially or completely substituted double bonds in excellent selectivity, superior to that displayed by the more classical Me_2CuLi. With hindered substrates, as generally observed in cuprate reaction, $Me_5Cu_3Li_2$ loses much of its selectivity, and this suggests that its use should be avoided in sterically crowded molecules.[98] The reagent lends itself, however, to the obtention of quaternary centers,[99] for which there is much interest in synthesis, and the versatile aldehydic group can be used in subsequent manipulations. We feel that the conjugate addition to enals can be of extreme value in assembling highly branched acyclic carbon skeletons, that are quite important in the field of natural product synthesis.[59] In this connection it must be noted that highly substituted α,β-unsaturated esters, which in principle could be used in lieu of aldehydes (and then, if necessary, reduced) do not undergo conjugate addition with cuprates in a synthetically useful way.[68]

The use of cuprates containing groups other than methyl probably deserves a detailed study. Normant[70b] has studied mainly dialkyl cuprates, with variable results; it still remains to be determined whether the use of more complex cuprates (e.g., do other $R_5Cu_3Li_2$ species exist in ether?) can turn the conjugate addition to α,β-unsaturated aldehydes into a widely general synthetic method.

In order to complete our original scheme [eq. (31), p. 38], we tried to perform some decarbonylation experiments on our methylated substrates, but we soon realized that these aldehydes are too hindered to be decarbonylated under mild conditions with Wilkinson's reagent.[80] In



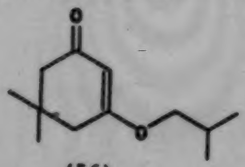
(45a) (55)

at 80°C: 9%
at 115°C: 20% (50)

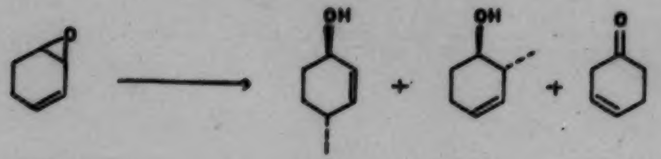
refluxing acetonitrile, the conversion of (45a) to (55) was exceedingly slow and even at 115°C [which is the b.p.

of (55)] in benzonitrile we obtained only a 20% conversion after an overnight reaction period. The reaction is, however, very clean and one can presumably bring the reaction to completion by working with less volatile compounds in refluxing (190°C) benzonitrile, but we felt that the vigorous thermal conditions required for this transformation make the overall process synthetically unattractive, although in principle viable.

$Me_5Cu_3Li_2$ has already been tested satisfactorily[85] in its conjugate addition to enones, but we were curious to see whether the new reagent could add to hardly reducible enones, i.e., enones to which Me_2CuLi fails to add. We made a sample of (56) (reduction potential:[71] -2.43 V), which is inert to Me_2CuLi. We found that $Me_5Cu_3Li_2$ too does not react with (56) even in ether-pentane and at a temperature of 0°C. It appears that, if $Me_5Cu_3Li_2$ is a more powerful reagent than Me_2CuLi in electron transfer processes, the difference in oxidation potentials is probably small.


(56)

Finally, we tested α,β-unsaturated epoxides as substrates for conjugate additions with $Me_5Cu_3Li_2$. The reaction of (57) with Me_2CuLi to give a 1:1 mixture of



(57) (57a) (57b) (57c)

(51)

(57a) and (57b) plus some elimination product (57c) has been described.[100] We found that $Me_5Cu_3Li_2$ gives exactly the same product distribution under analogous thermal and concentration conditions. It is likely that the features that make $Me_5Cu_3Li_2$ a good reagent for conjugate additions to enals do not have any effect in this case, since the reaction mechanism is likely to be completely different,[100] i.e., it probably does not involve electron transfer. Complex cuprates that show a high degree of selectivity in their addition to α,β-unsaturated epoxides have recently been described.[101]

EXPERIMENTAL PART

(A): General

Except where stated to the contrary, the following particulars apply. For reactions carried out under nitrogen, oven-dried glassware (130°C, 12-24 h) was used. The apparatus was allowed to cool in a desiccator or assembled hot, capped with rubber septa, and swept with nitrogen for *ca*. 15 min. Reactions were performed (after removal of the exit needle, unless gas was to be generated) under a slight static pressure of nitrogen. The nitrogen used had been purified by passage through a column (3.5 x 40 cm) of R-311 catalyst[102] and then through a similar column of Drierite. All solvents were distilled before use for chromatography. Solvents were dried, where specified, by distillation, under a static nitrogen atmosphere, from suitable desiccants and transferred *via* oven-dried syringes. Dry ether and THF were distilled from sodium (benzophenone indicator); dichloromethane, chloroform, deuterated chloroform, benzene, toluene, pentane, pyridine, acetonitrile and hexamethyl phosphoric triamide (HMPA) from calcium hydride [the latter under reduced pressure (0.1 mm)]; acetone from anhydrous potassium carbonate; methanol from magnesium methoxide. Benzonitrile was distilled under nitrogen. The following reagents were also dried before use and dispensed by syringe: thionyl chloride simply by distillation; triethylamine, chlorotrimethylsilane and diisopropylamine were distilled from calcium hydride. Magnesium turnings for Grignard reactions were rinsed with dry ether and dried at 130°C overnight prior to use. Cuprous iodide (Fisher) was purified by the literature method[84] and always stored under a nitrogen atmosphere. The commercial (Aldrich) solutions of methyllithium in ether, t-butyllithium in pentane and n-butyllithium in hexane where titrated, before use, by the diphenylacetic acid method.[103] Methylmagnesium bromide in ether (Aldrich) was titrated with chlorodimethylphenylsilane.[104]

Trimethylvinylsilane was commercially available (Petrarch) and was used without further purification.

Benzeneselenenyl chloride from Aldrich was found to be satisfactory for our purposes and was normally used as received. Triphenyltin hydride was made according to the literature[105] in small batches (10-20 g) and stored under nitrogen at -20°C for relatively short periods (up to 2-3 months). During product isolation, solutions were evaporated under water pump vacuum at room temperature. Where compounds were isolated simply by evaporation of their solutions, the residues were kept under oil pump vacuum and checked for constancy of weight. Isolated products were submitted directly for combustion analysis without need for additional purification, unless otherwise stated.

All vapor phase chromatography (VPC) analyses were performed on a Hewlett-Packard 5830A gas chromatograph equipped with an FID detector and, unless otherwise noted, with prepacked Hewlett-Packard 6 ft, 1/8" o.d. stainless steel analytical columns with nitrogen as the carrier gas. Columns used were: 10% DEGS on Chromosorb W, 80-100 mesh, 10% FFAP on Chromosorb W, 80-100 mesh and 10% APIEZON L on Chromosorb W, 80-100 mesh.

Yields were evaluated by VPC in the following way: a standard solution was prepared composed of the compounds to be analyzed plus an inert internal standard diluted with the appropriate solvent to the approximate concentration expected to occur from the reaction. Response factors of each component, compared to the internal standard, were calculated. The absolute yield of a specified component was then calculated by addition of a known amount of internal standard to the quenched solution of the reaction mixture, followed by VPC analysis. Commercial thin-layer chromatography (TLC) plates were used: silica was Camag type DF-B or Merck 60F-254; alumina was Camag type DSF-B or Merck 60F-254. Plates for preparative layer chromatography (PLC) were 60 x 20 x 0.1 cm and were heated at 110°C for 1 h before use. Silica gel for PLC was Merck type 60-PF-254. UV active spots were detected at 254 nm; spots detected by spraying with sulfuric acid (50% in methanol) were charred on a hot plate. Silica gel for column chromatography was Merck type 60, 70-230 mesh ASTM; silica gel for flash chromatography[39] was Merck type 60, 230-400 mesh ASTM. Silica gel for cyclofunctionalization reactions was Merck type 60-PF-254, and was dried at 115°-130°C overnight, then allowed to cool in a desiccator. Alumina for cyclofunctionalization reactions was Merck type GF-254 (60/E) and was similarly dried.

Infrared spectra were recorded on a Perkin-Elmer 297 infrared spectrophotometer; liquids and oils were usually run as neat films on sodium chloride plates, solids were run as solutions in the specified solvent, using 0.5 mm sodium chloride cells. Proton NMR spectra were recorded on Bruker WP-80 (at 80 MHz), Perkin-Elmer R32 (at 90 MHz), Varian HA-100 (at 100 MHz), Bruker WH-200 (at 200 MHz) or Bruker WH-400 (at 400 MHz) spectrophotometers, in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were recorded on a Bruker HFX-90 (at 22.6 MHz) spectrophotometer with deuterated chloroform as an internal standard. Mass spectra were recorded on an A.E.I. MS-50 mass spectrometer at an ionizing voltage of 70 eV.

For reactions run at 0°C, the reaction flasks were cooled in an ice water bath; lower temperatures were obtained by the use of dry ice-ethanol mixtures. Unless otherwise noted, stirring refers to the use of a Teflon coated magnetic bar. Melting points were determined on a Kofler block melting point apparatus. Boiling points quoted for products distilled in a Kugelrohr apparatus refer to the oven temperature.

(B): Cyclofunctionalization of unsaturated urethanes.

Preparation of unsaturated urethanes:

N-Carbethoxy-4-pentenylamine (1). 4-Pentenylamine[20] (1.45 g, 17.03 mmol) was dissolved in water (10 mL). Ethyl chloroformate (1.075 g, 9.91 mmol) was added and the mixture was shaken vigorously for about 5 min with intermittent cooling by immersion in a cold-water bath. A solution of sodium hydroxide (800 mg, 20 mmol) in water (5 mL) was added, followed immediately by more ethyl chloroformate (1.075 g, 9.91 mmol). The mixture was shaken vigorously for 15 min. It was then extracted with dichloromethane (2 x 30 mL) and the organic solution was dried (Na_2SO_4) and evaporated. Distillation of the residue gave 2.398 g (89%) of (1) as a colorless and homogeneous (vpc) oil: bp ~90°C (2.3 mm); NMR ($CDCl_3$, 100 MHz) δ 1.22 (t, J = 7 Hz, 3H), 1.4—1.8 (m, 2H), 1.88—2.32 (m, 2H), 3.16 (q, J = 6.5 Hz, 2H), 4.09 (q, J = 7 Hz, 2H), 4.6—6.0 (m, 4H); exact mass 157.1102 [calcd for $C_8H_{15}NO_2$, 157.1103]. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.10, H, 9.62; N, 8.94.

N-Carbethoxy-2-allylaniline (2). Ethyl chloroformate (0.66 mL, 6.90 mmol) and then sodium hydroxide (273 mg, 6.82 mmol) were added to a magnetically stirred and ice-cooled mixture of 2-allylaniline[26] (883.8 mg, 6.64

mmol) and water (12 mL). The cooling bath was removed after 5 min and stirring was continued for 1 h. The mixture was extracted with dichloromethane (30 mL) and the extract was washed with water (10 mL), dried (Na_2SO_4) and evaporated. Chromatography of the residue over silica gel (3 x 55 cm) with 1:3 ethyl acetate—heptane followed by Kugelrohr distillation (120°C, 0.1 mm) gave 1.150 g (84%) of (2) as a colorless solid: mp 45—46°C; NMR ($CDCl_3$, 100 MHz) δ 1.28 (t, J = 7.1 Hz, 3H), 3.22—3.47 (m, 2H), 4.16 (q, J = 7.1 Hz, 2H), 4.9—5.27 (m, 2H), 5.7—6.2 (m, 1H), 6.54 (br. s, 1H), 6.9—7.35 (m, 3H), 7.78 (br. d, J = ca. 8 Hz, 1H); exact mass 205.1101 [calcd for $C_{12}H_{15}NO_2$, 205.1099]. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.25; H, 7.31; N, 6.72.

N-Carbethoxy-2-(2-cyclohexenyl)aniline (3). Ethyl chloroformate (0.55 mL, 5.7 mmol) and sodium hydroxide (215 mg, 5.37 mmol) were added to a magnetically stirred and ice-cooled mixture of 2-(2-cyclohexenyl)aniline[7] (899.6 mg, 5.19 mmol) and water (10 mL). After the addition, the cooling bath was removed and stirring was continued for 1 h. The mixture was extracted with dichloromethane (3 x 15 mL) and the organic extract was washed with water (10 mL), dried (Na_2SO_4), and evaporated. Chromatography of the residue over silica gel (5 x 60 cm) with 1:4 ethyl acetate—heptane and Kugelrohr distillation (175°C, 0.8 mm) gave 1.099 g (86%) of (3) as a yellow, homogeneous (TLC, silica, 1:4 ethyl acetate—heptane) oil that solidified on standing: mp 38—39°C; NMR ($CDCl_3$, 100 MHz) δ 1.24 (t, J = 7 Hz, 3H), 1.3—2.4 (m, 6H), 3.5 (m, 1H), 4.16 (q, J = 7 Hz, 2H), 5.45—6.1 (m, 2H), 6.6—7.35 (m, 4H), 7.55—7.92 (m, 1H); exact mass 245.1414 [calcd for $C_{15}H_{19}NO_2$, 245.1415]. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.28; H, 7.66; N, 5.73.

2-Allylbenzoic acid (13). Magnesium turnings (16.7 g, 0.68 mol) were placed in a dry 2 L, 3-necked flask equipped with dropping funnel, mechanical stirrer and reflux condenser surmounted by a $CaSO_4$ drying tube. Dry ether (200 mL) was added and 1,2-dibromobenzene (153.9 g, 0.655 mol) in ether (200 mL) was added from the dropping funnel at such a rate as to maintain gentle reflux (1 h). After the end of the addition, the mixture was stirred and refluxed a further 50 min, then allyl bromide (82.0 g, 0.677 mol) in ether (100 mL) was added dropwise over 1.5 h. Stirring was maintained throughout. Further reflux (1.5 h), cooling, and quenching with ammonium chloride (17 g) in water (200 mL) was followed by separation of the ethereal phase, drying (Na_2SO_4) and evaporation at the water pump. The residue was subjected to spinning band distillation. The fraction boiling at 91°C, (14 mm) was collected and found to consist of two compounds by VPC (APIEZON L, 200°C); the first (retention time 7.92 min) was found to be 2-allylbromobenzene after VPC separation (40 ft x 1/4" o.d. APIEZON T 10% on Chromosorb W, column temperature 190°C, injection temperature 250°C). This sample had NMR ($CDCl_3$, 90 MHz) δ 3.2—3.6 (m, 2H), 4.8—5.2 (m, 2H), 5.7—6.3 (m, 1H), 6.9—7.6 (m, 4H).

The second component (retention time 9.53 min) was found to be 1,2-diallylbenzene after VPC separation (above conditions); NMR ($CDCl_3$, 90 MHz) δ 3.2—3.6 (m, 4H), 4.8—5.2 (m, 4H), 5.7—6.3 (m, 2H), 6.9—7.2 (m, 4H). By integration of the NMR signals of the distilled sample (52.48 g) it was established that it contained approximately 27.1 g 2-bromoallylbenzene (21% yield) and 25.4 g 1,2-diallylbenzene.

A portion of this sample (14.5 g, containing 2-allylbromobenzene, 7.49 g, 38.0 mmol) was added to a stirred, cooled (0°C) solution of butyllithium (2.4 M hexane solution, 15.83 mL, 38 mmol) in ether (20 mL) over a 30 min period, and stirred for a further 3 h at 0°C. It was then transferred by syringe onto a large excess (ca. 3 Kg) of solid CO_2 and left standing overnight. Addition of more ether (200 mL) and aqueous potassium hydroxide (10% w/v, 400 mL) was followed by separation of the aqueous phase. This was acidified (aqueous hydrochloric acid) and extracted with ether (2 x 300 mL), then dried (Na_2SO_4) and evaporated to afford (13) as a pale yellow solid (5.44 g, 88%) mp 77—82°C (lit.[106] 83—84°C), having NMR ($CDCl_3$, 100 MHz) δ 3.81 (d, J = 6 Hz, 2H), 4.8—5.2 (m, 2H), 5.7—6.3 (m, 1H), 7.0—7.7 (m, 3H), 7.9—8.1 (m, 1H), 12.2 (br. s, 1H).

2-Allylbenzamide (14). 2-Allylbenzoic acid (5.30 g, 32.7 mmol) in dry ether (40 mL) was treated with thionyl chloride (25 mL, 0.388 mol) and stirred at room temperature for 20 h with protection from moisture ($CaSO_4$ tube). The solution was evaporated and the residue dissolved in dry acetone (30 mL). This acetone solution was added slowly to a stirred, cooled (0°C) concentrated ammonium hydroxide solution (100 mL). After stirring for 1 h at room temperature, most of the acetone was evaporated at the water pump, and the residual aqueous solution was extracted with dichloromethane (2 x 200 mL). The organic phase was washed with aqueous sodium carbonate (5% w/v, 2 x 100 mL), water (100 mL) and dried (Na_2SO_4). Evaporation was followed by chromatography over silica gel (5 x 60 cm) with ethyl acetate. Recrystallization from ethyl acetate—heptane gave (14) (3.18 g, 60%) as

off-white needles, mp 119.5—123°C (lit.[106] 122-3°C). IR (CCl_4) 3370, 3175, 1645 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 3.55 (d, J = 6.4 Hz, 2H), 4.7—5.2 (m, 2H), 5.7—6.2 (m, 1H), 6.5 (br. s, 1H), 7.0—7.5 (m, 4H).

N-Carbethoxy-2-allylbenzylamine (4). 2-Allylbenzamide (14) (268.3 mg, 1.66 mmol) in ether (25 mL) was added dropwise to a magnetically stirred suspension of lithium aluminum hydride (212.6 mg, 5.60 mmol) in ether (5 mL). The mixture was refluxed for 48 h, cooled and diluted successively with water (0.2 mL), aqueous sodium hydroxide (15% w/v, 0.2 mL), and water (0.6 mL). The mixture was stirred with ice bath cooling during the course of this work-up and, after an additional 15 min, ethyl chloroformate (3 mL, 31.4 mmol) was added at a fast dropwise rate. Vigorous stirring was continued for 30 min and the mixture was filtered through a sintered disc. The insoluble material was washed liberally with ether and the combined filtrates were evaporated. Chromatography of the residue over silica gel (2 x 60 cm) with 1:4 ethyl acetate—heptane followed by Kugelrohr distillation (110°C, 0.05 mm) gave 284 mg (77%) of (4) as a colorless and homogeneous (TLC, silica, 1:4 ethyl acetate—heptane) liquid: NMR ($CDCl_3$, 100 MHz) δ 1.20 (t, J = 7 Hz, 3H), 3.39 (t of d, J_1 = 6 Hz, J_2 = 1.5 Hz, 2H), 4.11 (q, J = 7 Hz, 2H), 4.32 (br. d, J = 6 Hz, 2H), 4.6—5.4 (m, 3H), 5.65—6.15 (m, 1H), 7.0—7.4 (m, 4H); exact mass 219.1261 [calcd for $C_{13}H_{17}NO_2$, 219.1260]. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.02; H, 7.82; N, 6.37.

(2-Cyclopentenyl)acetamide (10). Anhydrous benzene (250 mL) was saturated with dry ammonia, the solution being stirred magnetically and cooled in a cold-water bath during this process. Passage of ammonia was continued and (2-cyclopentenyl)acetic acid chloride[107] (12.0 g, 82.99 mmol) was injected slowly from a syringe, the internal temperature of the reaction mixture being kept in the range 20—30°C. The ammonia stream was stopped 30 min after the end of the addition and the mixture was stirred for an additional 30 min. The mixture was shaken with water (300 mL) and the aqueous layer was extracted with ether (500 mL). The combined benzene and ether extracts were washed twice with saturated aqueous $NaHCO_3$ and then with brine. The organic phase was dried (Na_2SO_4) and evaporated to afford 5.58 g (53%) of (2-cyclopentenyl)acetamide (10): mp 128—133°C [lit.[108] mp 133°C]; NMR ($CDCl_3$, 100 MHz) δ 1.1—2.6 (m, 6H), 2.8—3.3 (br. t, J = *ca*. 7 Hz, 1H), 5.70 (m, 2H), *ca*. 5.0—7.0 [m (incorporating br. NH-signal); 2H]. The amide was used directly for the preparation of (5) and (6).

N-Carbethoxy-2-(2-cyclopentenyl)ethylamine (**5**). (2-Cyclopentenyl)acetamide (**10**) (1.030 g, 8.23 mmol) in dry THF (45 mL) was injected slowly into a vigorously stirred suspension of lithium aluminum hydride (2.00 g, 52.7 mmol) in THF (10 mL). The mixture was refluxed for 90 min and it was then cooled in ice. Successive portions of water (2 mL), aqueous sodium hydroxide (15% w/v, 2 mL), and water (6 mL) were added with stirring and, after a further 15 min, ethyl chloroformate (8 mL, 83.7 mmol) was injected dropwise. The cooling bath was removed and stirring was continued for 15 min. The resulting slurry was filtered through a sintered disc. The insoluble material was washed liberally with ether and the combined filtrates were evaporated. Chromatography of the residue over silica gel (5 x 65 cm) with 1:4 ethyl acetate—heptane and Kugelrohr distillation (118°C, 0.18 mm) gave 1.313 g (87%) of (**5**) as a colorless, homogeneous (TLC, silica, 1:4 ethyl acetate—heptane) liquid: IR (film) 1698 cm^{-1}; NMR (CDCl$_3$, 100 MHz) δ 1.0—2.5 [m, (incorporating t, $J = 7$ Hz at δ 1.22), 6H], 2.66 (br. t, $J =$ *ca*. 7.5 Hz, 1H), 3—3.4 (m, 2H), 4.10 (q, $J = 7$ Hz, 2H), 4.80 (br. s, 1H), 5.6—5.85 (m, 2H); exact mass 183.1258 [calcd for $C_{10}H_{17}NO_2$, 183.1267]. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.50; H, 9.28; N, 7.90.

1,1-d_2-N-Carbethoxy-2-(2-cyclopentenyl)ethylamine (6). This compound was prepared (83%) by the same method used for (5) except that lithium aluminum deuteride was employed in the reduction step. Compound (6) had: NMR ($CDCl_3$, 100 MHz) δ 1.0—1.8 [m, (incorporating t, J = 7.2 Hz, at 1.28 δ), 6H], 1.8—2.5 (m, 3H), 2.7 (br. t, J = *ca*. 6 Hz, 1H), 4.1 (q, J = 7.2 Hz, 2H), 4.86 (br. s, 1H), 5.5—5.9 (m, 2H); exact mass 185.1390 [calcd for $C_{10}H_{15}D_2NO_2$, 185.1385].

2-Undecylhept-6-enoic acid (12).[22] Butyllithium (2.4 M heptane solution, 20.9 mL, 50.16 mmol) was added dropwise, under nitrogen, to a magnetically stirred solution of dry diisopropylamine (4.90 g, 48.4 mmol) in THF (30 mL). The internal temperature of the reaction mixture was kept below -10°C by using an acetone—dry ice cooling bath. Tridecanoic acid (4.715 g, 22.00 mmol) in THF (30 mL) was injected 10 min after the end of the addition at such a rate that the cooling bath was able to maintain the temperature below 0°. Hexamethylphosphoric triamide (4.5 mL, from a freshly opened bottle) was added in one lot, the cooling bath was removed, and the mixture was stirred for 30 min. 5-Bromopentene[109] (3.615 g, 24.26 mmol) in THF (20 mL) was then injected very rapidly, causing the temperature of the mixture to rise from -5° to +5°. Stirring at room temperature was continued overnight. At that stage the mixture was diluted with hydrochloric acid (10% w/v, 100 mL) and extracted with petroleum ether (400 mL; bp 30—60°C). The organic solution was washed with hydrochloric acid (10% w/v, 3 x 100 mL) followed by brine and it was then dried (Na_2SO_4). Evaporation afforded 6.033 g (97%) of the product in a form sufficiently pure for the next stage. The material had: NMR ($CDCl_3$, 100 MHz) δ 0.65—2.7 (m, 30H), 4.8—5.2 (m, 2H), 5.55—6.0 (m, 1H), ca. 10 (br. s, 1H). A sample of the bulk product was analyzed. Anal. Calcd for $C_{18}H_{34}O_2$: C, 76.53; H, 12.13. Found: C, 76.39; H, 12.29.

N-Carbethoxy-6-amino-1-heptadecene (7).[23a] Thionyl chloride (40 mL) was added to a solution of 2-undecylhept-6-enoic acid (6.03 g, 21.35 mmol) in dry toluene (40 mL) and the mixture was stirred, with protection from moisture, for 3.5 h. At this stage formation of the acid chloride was complete (IR control) and the solvent and excess of reagent were evaporated *in vacuo* at room temperature. The residual acid chloride was dissolved in dry acetone (30 mL) and added to an ice-cold solution of sodium azide (7.0 g, 107.7 mmol) in water (50 mL). The resulting suspension was stirred at room temperature for 1 h, diluted with water (100 mL) and extracted with toluene (200 mL). The organic layer was washed with brine, dried (Na_2SO_4), and evaporated at room temperature. Caution.[110] The crude azide (ν_{max}^{film} 2135 cm^{-1}) was dissolved in dry toluene (100 mL) and the mixture was protected from moisture by a calcium sulfate tube and heated in a thermostatically controlled oil bath at 95°C for 3 h. At this stage all the azide had been converted into the corresponding isocyanate (ν_{max}^{film} 2270 cm^{-1}). Absolute ethanol (20 mL) was added, and heating at 95°C was continued for 40 h. During this period the isocyanate was converted into the ethyl carbamate (7) (IR control). The mixture was evaporated and the residual solid was subjected to flash chromatography over silica gel (5 x 16 cm) with 1:15 ethyl acetate—heptane to afford 2.718 g of (7) as a white, homogeneous (TLC, silica, 1:8 ethyl acetate—heptane) solid: mp 56—57°C. [An impure fraction (702 mg) was also obtained but was not processed further.] Recrystallization from methanol gave 2.499 g (35%) of (7). mp 61.5—63°C; IR (solid) 1684 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.65—2.35 (m, 32H), 3.55 (br. s, 1H), 3.85—4.55 [m, (incorporating q, J = 7 Hz at δ 4.08), 3H], 4.8—5.2 (m, 2H), 5.55—6.0 (m, 1H); exact mass 325.2977 [calcd for $C_{20}H_{39}NO_2$, 325.2981]. Anal. Calcd for $C_{20}H_{39}NO_2$: C, 73.79; H, 12.08; N, 4.30. Found: C, 73.66; H, 12.18; N, 4.20.

N-Carbethoxy-2-(3-methyl-2-butenyl)aniline (8).

2-(3-Methyl-2-butenyl)aniline[7] (310.7 mg, 1.93 mmol) was suspended in water (5 mL). The mixture was stirred magnetically in an ice bath and sodium hydroxide (90 mg, 2.25 mmol), followed immediately by ethyl chloroformate (0.22 mL, 2.3 mmol), was added. After a further 5 min the cooling bath was removed and stirring was continued for 1 h. The mixture was extracted with dichloromethane (30 mL) and the extract was washed with water (5 mL), dried (Na_2SO_4), and evaporated. The residual oil was chromatographed over silica gel (2 x 50 cm) with 1:1 ethyl acetate—heptane and then distilled (Kugelrohr, 120°C, 0.1 mm) to afford 408.4 mg (90%) of (8) as a colorless, homogeneous (TLC, silica, 1:2 ethyl acetate—heptane) liquid: NMR ($CDCl_3$, 100 MHz) δ 1.28 (t, J = 7 Hz, 3H), ca. 1.78 (br. s, 6H), 3.30 (br. d, J = 7.2 Hz, 2H), 4.20 (q, J = 7 Hz, 2H), 5.20 (t of m, 1H), 6.7 (br. s, 1H), 6.8—7.4 (m, 3H), 7.77 (br. d, J = 7.6, 1H); exact mass 233.1419 [calcd for $C_{14}H_{19}NO_2$, 233.1416]. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.03; H, 8.28; N, 5.86.

Cyclized Urethanes:

(±)-N-Carbethoxy-2-[(phenylseleno)methyl]pyrrolidine (1a).

Tri-n-butylphosphine (413 mg, 2.04 mmol) was injected dropwise over about 3 min into a magnetically stirred solution of (±)-N-carbethoxy-2-(hydroxymethyl)pyrrolidine (15)[111] (232 mg, 1.34 mmol) and phenylselenocyanate (282 mg, 1.54 mmol) in THF (2.5 mL).[30] The red solution was stirred under nitrogen for 2 h and it was then evaporated. Chromatography of the residue first over silica gel (1 x 50 cm) with 1:1 ethyl acetate—heptane and then over silica gel (1 x 50 cm) with 1:3 ethyl acetate—heptane followed by distillation in a Kugelrohr apparatus gave 87 mg (20%) of (1a) as a pale yellow, homogeneous (TLC, silica 1:3 ethyl acetate—heptane) oil: bp 130°C (0.15 mm); IR (CCl_4) 1700 cm^{-1}; NMR ($CDCl_3$; 32°C) δ 1.2 (t, J = 7 Hz, 3H), 1.5—2.11 (m, 4H), 2.44—3.06 (m, 1H), 3.06—3.6 (m, 3H), 3.74—4.3 [m (incorporating q, J = 7 Hz at 4.06 δ), 3H], 7.02—7.37 (m, 3H), 7.37—7.70 (m, 2H). Anal. Calcd for $C_{14}H_{19}NO_2Se$: C, 53.85; H, 6.13; N, 4.49; O, 10.25. Found: C, 53.61; H, 6.20; N, 4.58; O, 10.33.

General Procedure for Cyclofunctionalizations: (Reaction times are specified in Table 2).

N-Carbethoxy-2[(phenylseleno)methyl]pyrrolidine (1a). N-Carbethoxy-4-pentylamine (1) (378.5 mg, 2.41 mmol) and silica gel (735 mg) were weighed into a dry round-bottomed flask. A magnetic stirring bar was added and the flask was closed by a rubber septum carrying inlet and exit needles for nitrogen. Dry dichloromethane (10 mL) was injected and the resulting suspension was stirred and cooled by an acetone—dry ice bath at -78°C. Benzeneselenenyl chloride (514.4 mg, 2.69 mmol) in dichloromethane (8 mL) was added dropwise, the addition taking ca. 20 min. The red color of each drop was discharged instantaneously. More solvent (2 mL) was used to rinse all the reagent into the reaction vessel. The exit needle for nitrogen was removed and vigorous stirring was continued first for 10 min with the cooling bath in place and then for 75 min without the bath. During the latter period the reaction flask was wrapped with aluminum foil. The yellow suspension was filtered through a sintered disc and insoluble material was washed with ethyl acetate. The combined filtrates were evaporated and the residue was chromatographed over silica gel (2 x 57 cm) with 1:4 ethyl acetate—heptane. When the diphenyl diselenide had been eluted the solvent was changed to 1:1 ethyl acetate—heptane. Appropriate fractions were combined, evaporated and distilled in a Kugelrohr apparatus (130°C, 0.01 mm) to afford 706.2 mg (93%) of (1a) as a yellow, homogeneous (TLC, silica, 1:3 ethyl acetate—heptane) oil spectroscopically identical with material made from racemic proline. The present sample had: IR (film) 1700 cm^{-1}; NMR ($CDCl_3$, 100 MHz,

0°C) δ 1.04—1.4 (two overlapping t, J = 7.1 Hz, 3H), 1.57—2.12 (m, 4H), 2.49—3.0 (m, 1H), 3.09—3.72 (m, 3H), 3.72—4.36 [m (incorporating q, J = 7 Hz at 4.06 δ), 3H], 7.04—7.39 (m, 3H), 7.39—7.75 (m, 2H); exact mass 313.0581 [calcd for $C_{14}H_{19}NO_2{}^{80}Se$, 313.0581].

N-Carbethoxy-2,3-dihydro-2-[(phenylseleno)methyl]indole (2a).

The general method was followed using *N*-carbethoxy-2-allylaniline (2) (76.7 mg, 0.374 mmol) and silica gel (85.0 mg) in dichloromethane (1 mL) together with benzeneselenenyl chloride (74.8 mg, 0.391 mmol) in dichloromethane (1 mL plus 0.5 mL as a rinse). After a reaction period of 24 h at room temperature work-up in the standard way and isolation by PLC (one silica plate developed with 1:5 ethyl acetate—heptane) followed by distillation in a Kugelrohr apparatus (203°C, 0.13 mm) gave 114.9 mg (85%) of (2a) as a homogeneous (TLC, silica, 1:4 ethyl acetate—heptane) oil: IR (film) 1703 cm^{-1}; NMR ($CDCl_3$, 100 MHz, 32°C) δ 1.3 (t, J = 7.1 Hz, 3H), 2.64—3.52 (m, 4H), 4.29 (q, J = 7.1 Hz, 2H), 4.37—4.72 (m, 1H), 6.73—7.90 (m, 9H); exact mass 861.0607 [calcd for $C_{18}H_{19}NO_2{}^{80}Se$, 361.0581]. Anal. Calcd for $C_{18}H_{19}NO_2Se$: C, 60.00; H, 5.31; N, 3.89; O, 8.88. Found: C, 60.22; H, 5.37; N, 3.83; O, 8.91.

In an alternative procedure, alumina (Merck type E, PF-254, oven-dried at 130°C overnight) was employed instead of silica gel as follows: The general method was followed using (2) (113.7 g, 0.554 mmol) and alumina (403 mg) in dichloromethane (2 mL) together with benzeneselenenyl chloride (115.5 mg, 0.603 mmol) in dichloromethane (3 mL plus 1 mL rinse). After a reaction period of 17 h at room temperature, work-up as usual and isolation by PLC (as above) followed by Kugelrohr distillation (190°C, 0.07 mm) gave 176.0 mg (88%) of (2a), identical (TLC, IR, NMR) with the sample obtained in the run employing silica gel.

(1α,4aα,9aα)-9-Carbethoxy-1-(phenylseleno)-1,2,3,4,4a,9a-hexahydrocarbazole (3a). The general method was followed using N-carbethoxy-2-(2-cyclohexenyl)aniline (3) (265.0 mg, 1.08 mmol) and silica gel (1.020 g) in dichloromethane (5 mL) together with benzeneselenenyl chloride (234.2 mg, 1.22 mmol) in dichloromethane (2 mL plus 1 mL as a rinse). After a reaction period of 24 h at room temperature work-up in the standard way and chromatography over silica gel (3 x 60 cm) with 1:9 ethyl acetate—heptane followed by crystallization from methanol gave 355.1 mg (82%) of (3a) as a white, homogeneous (TLC, silica, 1:4 ethyl acetate—heptane) solid: mp 99—100°C; IR (solid) 1704 cm^{-1}; NMR ($CDCl_3$, 100 MHz, 32°C) δ 1.0—2.3 [m, (incorporating t, J = 7 Hz at 1.23 δ) 9H], 3.11 (t of d, br, $J_1 = 10$, $J_2 = 4$ Hz, 1H), 3.54 (br. t, J = 6Hz, 1H), 4.2 (q, J = 7 Hz, 2H), 4.54 (d of d, J_1 = 7.5 Hz, J_2 = 9 Hz, 1H), 6.8—7.8 (m, 9H); exact mass 401.0902 (calcd for $C_{21}H_{23}NO_2{}^{80}Se$, 401.0894). Anal. Calcd for $C_{21}H_{23}NO_2Se$: C, 63.00; H, 5.79; N, 3.50; O, 7.99. Found: C, 62.95; H, 5.56; N, 3.35; O, 8.15.

2-Carbethoxy-3-[(phenylseleno)methyl]-1,2,3,4-tetrahydroisoquinoline (4a). The general method was followed using N-carbethoxy-2-allylbenzylamine (4) (212.4 mg, 0.97 mmol) and silica gel (389 mg) in dichloromethane (3 mL) together with benzeneselenenyl chloride (201.3 mg, 1.05 mmol) in dichloromethane (2 mL and 1 mL as a rinse). After a reaction period of 16 h at room temperature work-up in the standard way and chromatography over silica gel (3 x 50 cm) with 1:5 ethyl acetate—heptane followed by Kugelrohr distillation (200°C, 0.1 mm) gave 315.6 mg (87%) of (4a) as a pale yellow, homogeneous (TLC, 1:5 ethyl acetate—heptane) oil: IR (film) 1701 cm^{-1}: NMR ($CDCl_3$, 100 MHz, 31°C) δ 1.23 (br. t, J = 6.5 Hz, 3H), 2.55—3.24 (m, 3H), 3.95—4.9 (m, 5H), 6.8—7.65 (m, 9H); exact mass 375.0739 (calcd for $C_{19}H_{21}NO_2{}^{80}Se$, 375.0739). Anal. Calcd for $C_{19}H_{21}NO_2Se$: C, 60.96; H, 5.65; N, 3.74. Found: C, 60.93; H, 5.64; N, 3.59.

(3aα,6α,6aα)-1-Carbethoxy-6-(phenylseleno)octahydrocyclopenta[b]pyrrole (5a). The general method was followed using N-carbethoxy-2-(2-cyclopentenyl)ethylamine (5) (320 mg, 1.75 mmol) and silica gel (290 mg) in dichloromethane (3 mL) together with benzeneselenenyl chloride (367 mg, 1.92 mmol) in dichloromethane (4 mL plus 1 mL as a rinse). After an overnight reaction period at room temperature work-up in the standard way and chromatography over silica gel (2 x 60 cm) with 1:4 ethyl acetate—heptane followed by Kugelrohr distillation (180°C, 0.1 mm) afforded 556.1 mg (94%) of (5a) as a yellow, homogeneous (TLC, silica, 1:4 ethyl acetate—heptane) oil: IR (film) 1699 cm^{-1}; NMR (DMSO-d_6, 200 MHz, 70°C) δ 1.12 (t, J = 7 Hz, 3H), 1.26—2.2 (m, 6H), 2.74—2.98 (m, 1H), 3.07—3.29 (m, 1H), 3.54 (2 partially overlapping q, J_1 = 11.2 Hz, J_2 = 8.3 Hz, J_3 = 3.2 Hz), 3.89 (br. s, $w_{1/2}$ = 11 Hz), 3.99 (q of d, J_1 = 8 Hz, J_2 ca. 1 Hz), 4.12 (br. d, J = 7 Hz), [signals at 3.8—4.2 represent 4H], 7.22—7.4 (m, 3H), 7.5—7.66 (m, 2H); exact mass 339.0734 (calcd for $C_{16}H_{21}NO_2{}^{80}Se$, 339.0738). Anal. Calcd for $C_{16}H_{21}NO_2Se$: C, 56.80; H, 6.26; N, 4.14; O, 9.46. Found: C, 56.62; H, 6.17; N, 3.94; O, 9.21.

2,2-d_2-(3aα,6α,6aα)-1-Carbethoxy-6-(phenylseleno)octahydrocyclopenta[b]pyrrole (6a). 1,1-d_2-N-Carbethoxy-2(2-cyclopentenyl)ethylamine (6) was converted (83% yield), by the method used for the non-deuterated material, although on a smaller scale, into (6a) NMR (DMSO-d_6, 400 MHz, 70°C) δ 1.15 (t, J = 7 Hz, 3H), 1.36—1.5 (m, 1H), 1.59 (q, J_1 = 13 Hz, J_2 = 2 Hz, 1H), 1.64—1.77 (m, 1H), 1.88 (d of d, J_1 = 12 Hz, J_2 = 8 Hz, 1H), 1.93—2.1 (m, 2H), 2.8—2.96 (m, 1H), 3.88 (br. s, $w_{1/2}$ = 12.4 Hz, 1H), 3.92—4.07 (m, 1H), 4.12 (br. d, J = 6.5 Hz, 1H), 7.2—7.36 (m, 3H), 7.52—7.66 (m, 2H); exact mass 341.0864 (calcd for $C_{16}H_{19}D_2NO_2{}^{80}Se$, 341.0863).

N-Carbethoxy-*cis*-cyclopentano[b]pyrrolidine (18).

(a) 2-Oxo-*cis*-cyclopentano[b]pyrrolidine[112] (121.1 mg, 0.97 mmol) in dry ether (7 mL) was added over about 5 min to a magnetically stirred suspension of lithium aluminum hydride (190 mg, 5 mmol) in ether (4 mL). The mixture was refluxed under nitrogen for 3 h, cooled in an ice bath and diluted, with stirring, by successive portions of water (0.2 mL), 15% w/v aqueous sodium hydroxide (0.2 mL), and water (0.6 mL). The ice bath was removed for 15 min and then replaced. Ethyl chloroformate (1.13 g, 10.4 mmol) was added dropwise, the ice bath was removed and stirring was continued for 30 min. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (2 x 17 cm) with 1:4 ethyl acetate—heptane followed by distillation in a

Kugelrohr apparatus (95°C, 0.25 mm) gave 109.9 mg (62%) of the product as a colorless, homogeneous (TLC, silica, 1:4 ethyl acetate—heptane) oil identical with a fully characterized sample made by reduction of (5a) with triphenyltin hydride as follows:

(b) (3aα,6α,6aα)-1-Carbethoxy-6-(phenylseleno)octahydrocyclopenta[b]pyrrole, (18) (418.5 mg, 1.237 mmol) was dissolved in toluene (6 mL). The mixture was stirred magnetically and refluxed by using an oil bath maintained at 120°C. Triphenyltin hydride (1.1788 g, 3.358 mmol) was added by syringe. The syringe was rinsed with toluene (1 mL) and the rinse was added to the reaction mixture. Reflux was maintained for a further 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm) with 15:85 ethyl acetate—heptane gave, after Kugelrohr distillation (95°C, 0.25 mm), (18) as a colorless oil (222.1 mg, 98.0%). The product had IR (CCl_4) 1707 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7 Hz, 3H), 1.31—2.1 (m, 8H), 2.65 (m, 1H made of 9 lines, upon irradiation at δ 4.13 it collapsed to 7 lines, with loss of a coupling of 7.5 Hz), 3.20—3.40 (m, 1H), 3.40—3.67 (br. s, 1H), 4.0—4.27 (m, 3H, incorporating q centered at δ 4.13, J = 7 Hz); exact mass 183.1259 (calcd for $C_{10}H_{17}NO_2$, 183.1258). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.27; H, 9.32; N, 7.37.

cis-N-Carbethoxy-2-(phenylselenomethyl)-6-undecylpiperidine (7a). The general method was followed using N-carbethoxy-6-amino-1-heptadecene (7) (360.7 mg, 1.106 mmol) and silica gel (950 mg) in dichloromethane (12 mL) together with benzeneselenenyl chloride (236.1 mg, 1.232 mmol) in dichloromethane (2.5 mL plus 0.5 mL as a rinse). After a reaction period of 40 h at room temperature the mixture was filtered and the insoluble material was washed with ethyl acetate. The combined filtrates were evaporated and the residual yellow oil was subjected to flash chromatography over silica gel (3 x 18 cm). Heptane was used to elute diphenyl diselenide and elution was then continued with 1:4 ethyl acetate—heptane to afford 449.9 mg (84%) of (7a) as a homogeneous (TLC, silica or alumina, 1:9 ethyl acetate—heptane) oil: IR (film) 1693 cm^{-1}; NMR (DMSO-d_6, 70°C, 200 MHz) δ 0.85 (t, J = 6.50, 3H), 1.0—2.0 [m (incorporating t, J = 7 Hz at 1.09 δ, 24H), 2.96—3.24 (m, 2H), 3.88—4.13 [m, (incorporating d of q, J_1 = 7.0 Hz, J_2 = 2.8 Hz, at 3.99 δ), 3H], 4.13—4.34 (m, 1H), 7.2—7.4 (m, 3H), 7.44—7.6 (m, 2H); exact mass 481.2449 (calcd for $C_{26}H_{43}NO_2{}^{80}Se$, 481.2459). Anal. Calcd for $C_{26}H_{43}NO_2Se$: C, 64.98; H, 9.02; N, 2.91; O, 6.66. Found: C, 65.21; H, 9.18; N, 2.95; O, 6.51.

cis-*N*-Carbethoxy-2-methyl-6-undecylpiperidine (*29*).

cis-*N*-Carbethoxy-2-(phenylselenomethyl)-6-undecylpiperidine (*7a*) (631 mg, 1.313 mmol) was dissolved in toluene (12 mL). The mixture was stirred magnetically and refluxed by using an oil bath maintained at 120°C. Portions of triphenyltin hydride were injected from a syringe as follows, all the material being rinsed from the syringe after each injection by a small amount (*ca*. 1 mL) of toluene: 409 mg (1.165 mmol) as soon as reflux started; 313 mg (0.892 mmol) after 0.5 h; 630 mg (1.795 mmol) after 2.5 h; and 400 mg (1.139 mmol) after 5 h. Refluxing was continued for a further 19 h by which stage no starting material was detectable (TLC). Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 15 cm) with 1:99 ethyl acetate—heptane gave 414 mg (96%) of (*29*) as a faintly yellow oil. Examination by TLC revealed traces of uv-active impurities judged by NMR to amount to less than 2 mol % (assuming the impurity signals are due to triphenyltin groups). FT-IR (film) 1695 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.72—2.0 (m, 35H), 3.94—4.57 (br. signal overlapping q, J = 7 Hz at 4.13 δ, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.7, 20.5, 22.7, 27.5, 27.6, 29.4, 29.7, 30.3, 31.9, 35.1, 45.9, 50.5, 60.8, 156.2; exact mass, 310.2751 [calcd for $C_{19}H_{36}NO_2$ (M-CH_3), 310.2745]. Anal. Calcd for $C_{20}H_{39}NO_2$: C, 73.80; H, 12.08; N, 4.30. Found: C, 74.03; H, 12.12; N, 4.30.

cis-2-Methyl-6-undecylpiperidine (*19*). *cis*-*N*-Carbethoxy-2-methyl-6-undecylpiperidine (*29*) (140.4 mg, 0.431 mmol) was stirred with 95% ethanol (7 mL) and concentrated hydrochloric acid (8 mL). The mixture was refluxed for 88 h, cooled and evaporated. The residue was diluted with water, made strongly basic with sodium hydroxide, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 x 17 cm) with 1:5 ethyl acetate—heptane gave 100.4 mg (71.5%) of starting material. Elution was continued with ethanol containing 2% w/v concentrated ammonia solution to afford 29.1 mg [26.6% (93.4% afer correction for recovered starting material)] of (*19*) as a pale yellow, homogeneous (TLC, alumina, 1:7 ethyl acetate—heptane) oil: NMR ($CDCl_3$, 200 MHz) δ 0.81 (t, J = 6.4 Hz, 3H), 0.94—1.86 (m, 29H), 2.45—2.87 (m, 2H), *ca*. 4.4 (br. signal, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.1, 22.7, 24.8, 26.0, 29.3, 29.6, 31.7, 31.9, 34.0, 36.9, 52.7, 57.3; exact mass, 253.2755 (calcd for $C_{17}H_{35}N$, 253.2770), 238.2531 [calcd for $C_{16}H_{32}N$ ($M-CH_3$), 238.2535], 98.0966 [base peak, calcd for $C_6H_{12}N$ ($M-C_{11}H_{23}$), 98.0969]. The amine was converted into its hydrochloride (by passing hydrogen chloride into an ethereal solution) which was recrystallized twice from 1:10 ethanol—hexane: mp 153—155°C [lit.[34] 154-155°C].

N-Carbethoxy-2,3-dihydro[(1-methyl-1-phenylseleno)ethyl]-indole (8a) and N-Carbethoxy-2,2-dimethyl-3-(phenylseleno)-1,2,3,4-tetrahydroquinoline (8b). Apart from the presence of propylene oxide as an acid trap, the general method was followed: Benzeneselenenyl chloride (191.1 mg, 0.99 mmol) in dichloromethane (2.5 mL plus 0.5 mL as a rinse) was added at -78°C to a stirred mixture of N-carbethoxy-2-(3-methyl-2-butenyl)aniline (8) (214 mg, 0.92 mmol), propylene oxide (1 mL), and silica gel (572 mg) in dichloromethane (5 mL). After the usual 10 min reaction period, the cooling bath was removed and stirring in the dark was continued for 70 h. The mixture was filtered, the silica gel was washed liberally with ethyl acetate and the combined filtrates were evaporated. A chromatographically homogeneous (TLC, silica, 3:1 benzene—heptane) product weighing 271.1 mg (76%) was isolated by PLC (2 silica plates, developed once with 3:1 benzene—heptane). The NMR spectrum showed the material to be a mixture of (8a) and (8b) in the ratio of ca. 51:49. NMR ($CDCl_3$, 100 MHz, 30°C): (δ values for (8a) are quoted first): 1.02 (s), 1.2 (t, J = 7.2 Hz), 1.42 (s), [signals at 1.02—1.42 represent 9H], 3.25—3.47 (br. d, J = ca. 5.5 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 4.6 (d of d, J_1 = ca. 5 Hz, J_2 = 6.3 Hz, 1H). δ values for (8b) 1.25 (t, J = 7 Hz, 3H), 1.68 (s, 3H), 1.80 (s, 3H), 2.89—3.28 (m, 2H), 4.2 (q, J = 7 Hz, 2H). The NMR spectrum of the mixture also showed a m at 6.78—7.81 (9H). The material was characterized further by reduction with triphenyltin hydride. The material (50 mg) was recovered unchanged after a 140 h period of stirring at room temperature in dichloromethane (10 mL) with silica (100 mg).

N-Carbethoxy-2,3-dihydro-2-[(1-methyl)ethyl]indole (24) and N-Carbethoxy-2,2-dimethyl-1,2,3,4-tetrahydroquinoline (25). Triphenyltin hydride (698 mg, 1.99 mmol was added to a solution of (8a) and (8b) (235.9 mg combined weight, 0.61 mmol) in toluene (5 mL). The mixture was refluxed for 4.5 h (nitrogen atmosphere), cooled, filtered through a small pad of glass wool, and evaporated. The resulting grey slurry was distilled in a Kugelrohr apparatus (130°C, 0.1 mm) to afford a colorless liquid which was chromatographed over silica gel (2 x 55 cm) with 1:15 ethyl acetate—heptane to give 116.3 mg (82%) of (24) and (25) as a chromatographically homogeneous (TLC, silica, 1:15 ethyl acetate—heptane) oil. The two components were separated by preparative vpc [40 ft. x 1/4" o.d. Apiezon T 10% on Chromosorb W; column temperature 180°C; injection temperature 250°C]. Compound (25): IR (film) 1700 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.28 (t, J = 7 Hz, 3H), 1.6 (s, 6H), 1.65—1.86 (m, 2H), 2.5—2.7 (m, 2H), 4.22

(q, J = 7 Hz, 2H), 6.9—7.35 (m, 4H); exact mass 233.1415 (calcd for $C_{14}H_{19}NO_2$, 233.1419). Compound (24): IR (film) 1706 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 0.8 (d, J = 7 Hz, 3H), 0.9 (d, J = 7 Hz, 3H), 1.34 (t, J = 7 Hz, 3H), 2—2.5 (m, 1H), 2.6—3.35 (m, 2H), 3.95—4.55 [m (incorporating q, J = 7 Hz, at 4.3 δ), 3H], 6.65—7.4 (m, 3H), 7.5—7.85 (m, 1H); m/e (rel. intensity) 233 (13.9), 190 (47), 162 (3), 118 (100), 91 (15). The composition of the mixture before vpc separation was *ca*. 45% (24) and 55% (25) as judged by NMR.

NMR studies:

(i) (1):*N*-Carbethoxy-4-pentenylamine (1) (30.9 mg, 0.196 mmol) in dry $CDCl_3$ (0.5 mL) in a 5 mm NMR tube that was cooled to -75°C, was treated dropwise, with shaking, with benzeneselenenyl chloride (38.0 mg, 0.198 mmol) in dry $CDCl_3$ (0.5 mL plus 0.2 mL rinse), and the resulting reaction was monitored by NMR (100 MHz) within the temperature interval -50°C to room temperature for 2 h and at room temperature for 2 h. The observations are summarized in the discussion.

(ii) (8):*N*-Carbethoxy-2-(3-methyl-2-butenyl)aniline (8) (24.4 mg, 0.105 mmol) in dry $CDCl_3$ (0.3 mL) in a 5 mm NMR tube at -75°C was treated with benzeneselenenyl chloride (21.0 mg, 0.11 mmol) in $CDCl_3$ (0.5 mL plus 0.3

0.3 mL rinse) with shaking. The reaction was monitored by NMR (100 MHz) within the temperature interval -50°C to room temperature over _ca_. 2 h and at room temperature over _ca_. 24 h. After _ca_. 1 h at -50°C, the NMR data were consistent with a single species, identified as _N_-carbethoxy-2-(3-chloro-3-methyl-2-phenylseleno)aniline (26) having: NMR ($CDCl_3$, 100 MHz): δ 1.25 (t, J = 7 Hz, 3H), 1.76 (s, 3H), 1.81 (s, 3H), 2.81 (d of d, J_1 = 15 Hz, J_2 = 12 Hz, 1H), 3.19 (d, J = 12 Hz, 1H), 3.65 (d, J = 15 Hz, 1H), 4.18 (q, J = 7 Hz, 2H), 6.7—7.9 (m, 9H). The NMR spectrum was essentially unchanged up to room temperature for 2—3 h, then (8a) became apparent. After 15 h at room temperature (26) and (8a) were present in a ratio of approximately 7:3 [by integration of singlets at δ 1.76 and 1.81 for (26) and at δ 1.02 and 1.42 for (8a)]. On further standing at room temperature the mixture became slightly cloudy, the NMR spectrum (broad lines) did not appear different. After a total of 106 h at room temperature the mixture was filtered [cotton wool; dichloromethane rinse] and evaporated to afford an oil having a complex NMR spectrum which indicated (26) and (8a) in equal proportions to be present as well as a little (8b) and other, unidentified, impurities.

Cyclization attempts on (8):

(i) To a stirred, cooled (-50°C) solution of N-Carbethoxy-2-(3-methyl-2-butenyl)aniline (8) (124.3 mg, 0.533 mmol) in dry dichloromethane (5 mL), benzeneselenenyl chloride (123.1 mg, 0.642 mmol) in dichloromethane (1 mL plus 1 mL rinse) was added (main portion over 5 min). The yellow solution was stirred for a further 30 min at -50°C, then allowed to reach room temperature (over *ca*. 30 min) and stirred for a further 30 min. Evaporation gave a crude oil which was shown [TLC (silica, 1:4 ethyl acetate—heptane)] to consist of diphenyl diselenide, some starting material, only traces of cyclized products [(8a) and/or (8b)], and a major product with Rf = 0.25. Flash chromatography over silica gel (2 x 18 cm) using 1:8 ethyl acetate—heptane gave a pure (TLC, silica, 1:4 ethyl acetate—heptane) sample of N-carbethoxy-2-(3-hydroxy-3-methyl-2-phenylseleno)-aniline (27) (110.4 mg, 53.3%) having NMR ($CDCl_3$, 200 MHz) δ 1.28 (t, J = 7.0 Hz, 3H), 1.38 (s, 3H), 1.42 (s, 3H), 1.75 (br. s, 1H), 2.89 (d of d, J_1 = 14.4 Hz, J_2 = 10.8 Hz, 1H), 3.07 (d of d, J_1 = 10.8 Hz, J_2 = 2.0 Hz, 1H), 3.36 (d of d, J_1 = 14.4 Hz, J_2 = 2.0 Hz, 1H), 4.16 (d, J = 7.0 Hz, 2H), 7.0—7.3 (m, 8H), 7.40 (br. s, 1H), 7.75 (br. d, J = *ca*. 8 Hz, 1H); NMR (DMSO-d_6, 100 MHz) δ 1.1—1.4 (m, 9H), 2.89 (d of d, J_1 = *ca*. 14.5 Hz,

J_2 = *ca*. 11 Hz, 1H), 3.15 (br. d, J = *ca*. 11 Hz, 1H), 3.45 (br. d, J = *ca*. 14.5 Hz, 1H), 4.09 (q, J = 7 Hz, 2H), 4.90 (s, 1H), 6.80—7.55 (m, 9H), 8.70 (br. s, 1H); exact mass 407.1005 (calcd for $C_{20}H_{25}NO_3{}^{80}Se$, 407.0999).

(ii) To a stirred, cooled (-50°C) solution of *N*-carbethoxy-2-(3-methyl-2-butenyl)aniline (*8*) (100 mg, 0.429 mmol) in dichloromethane (5 mL), benzeneselenenyl chloride (103.5 mg, 0.540 mmol) in dichloromethane (1 mL plus 2 x 1 mL rinse) was added dropwise (main portion over 5 min). After a further 45 min at -50°C, the mixture was allowed to reach room temperature (*ca*. 30 min), evaporated and chromatographed over silica gel (3.5 x 70 cm) using dichloromethane. A TLC-pure (silica, dichloromethane) mixture of (*8a*) and (*8b*) (3:1 by NMR, 108.3 mg, 65%) was obtained. Kugelrohr distillation on a 60.0 mg sample (210°C, 0.1 mm) gave 55.4 mg (92.3% recovery, 60% overall cyclization yield) of (*8a*) and (*8b*), still in a 3:1 ratio (NMR, 100 MHz). A portion of this sample (35 mg) in dichloromethane (5 mL) was stirred for 75 h in the presence of dry silica gel (305 mg). Filtration and evaporation gave a mixture of (8a) and (8b), (36 mg, 100%) pure by TLC (above conditions), still in the ratio of 3:1 (NMR, 100 MHz).

(iii) To a stirred, cooled (-50°C) mixture of *N*-carbethoxy-2-(3-methyl-2-butenyl)aniline (*8*) (98 mg, 0.420 mmol), dry silica (163.9 mg) and dichloromethane (2 mL), benzeneselenenyl chloride (92.0 mg, 0.480 mmol) in dichloromethane (2 mL plus 1 mL rinse) was added (main portion over 5 min). The cold bath was removed and the suspension stirred overnight. Evaporation and PLC (one silica plate, 1:4 ethyl acetate—heptane) gave a crude sample of (8a) (96.4 mg, 59.1%, containing little, if any, (8b)) which was not processed further, and, as a major side-product, N-carbethoxy-2-(3-chloro-2-methylbutyl)-aniline (15.6 mg, 14%): NMR ($CDCl_3$, 100 MHz) δ 1.25 (t, J = 7 Hz, 3H), 1.58 (s, 6H), 1.7—2.0 (m, 2H), 2.6—2.85 (m, 2H), 4.15 (q, J = 7 Hz, 2H), 6.55 (br. s, 1H), 7.0—7.3 (m, 3H), 7.75 (br. d, J = ca. 8 Hz, 1H); m/e (rel. intensity) 269 (42.4), 233 (32.8), 160 (100), 146 (43.3), 132 (90.2).

(iv) To a cooled (-75°C), stirred suspension of N-carbethoxy-2-(3-methyl-2-butenyl)aniline (119.7 mg, 0.514 mmol) and dry alumina (378.1 mg) in dichloromethane (3 mL), benzeneselenenyl chloride (105.3 mg, 0.550 mmol) in dichloromethane (2 mL plus 1 mL rinse) was added (main portion over 5 min). The cold bath was then removed and the mixture allowed to attain room temperature, and stirred overnight (ca. 22 h). Filtration through a sintered disc and evaporation, followed by PLC (one silica plate with 3:1 benzene—heptane) gave unreacted (8) (110.7 mg, 92.5% recovery) as a pale yellow oil, identical

(NMR) with an authentic sample.

(v) To a stirred, cooled (-50°C) solution of *N*-carbethoxy-2-(3-methyl-2-butenyl)aniline (8) (111 mg, 0.476 mmol) in dichloromethane (3 mL), benzeneselenenyl chloride (111 mg, 0.58 mmol) in dichloromethane (2 mL plus 1 mL rinse) was added (main portion over *ca*. 5 min). The cold bath was then removed and, after an overnight period at room temperature, evaporation and flash chromatography over silica gel (3 x 18 cm) using 1:60 ethyl acetate—heptane gave a crude mixture of (8a) and (8b) (98 mg, 53%, *ca*. 7:3 by NMR).

(C): Reactions of Vinylsilanes with Selenium Electrophiles.

2-Phenylseleno-2-trimethylsilyl ethanol (38).[113] Silver trifluoroacetate (846 mg, 3.830 mmol) in dry THF (5 mL) was treated dropwise under nitrogen with benzeneselenenyl chloride (608 mg, 3.174 mmol) in THF (3 mL plus 1 mL rinse) over 10 min. After a further period of 5 min at room temperature with magnetic stirring, the thick suspension was cooled to -75°C and treated with trimethylvinylsilane (37) (308 mg, 3.073 mmol) in THF (2 mL). After 10 min the cold bath was removed and the mixture was stirred 2 h at room temperature with protection from light. The silver chloride was then filtered off through a Celite pad (5 x 2 cm) and the pad washed with more THF (2 x 20 mL). The filtrate was evaporated and redissolved in methanol (20 mL).

Sodium hydrogen carbonate (1.65 g, 19.64 mmol) and water (5 mL) were added and the mixture was stirred overnight at room temperature. Most of the methanol was then cautiously evaporated at the rotary evaporator, and ether (50 mL) and water (50 mL) were added to the residue. The organic phase was separated, washed with brine (50 mL) and dried (Na_2SO_4). Evaporation followed by flash chromatography over silica gel (3 x 17 cm) with heptane containing increasing amounts (8%—25% v/v) of ethyl acetate, gave (38) (686.1 mg, 81.7%) as a colorless oil, pure by TLC (silica, 1:5 heptane—ethyl acetate): IR (film) 3350 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 9H), 2.30 (br. s, 1H), 2.64 (d of d, J_1 = 6.2 Hz; J_2 = 4.0 Hz, 1H), 3.80 (m, 2H), 7.2—7.3 (m, 3H), 7.5—7.65 (m, 2H); NMR (DMSO-$\underline{d}_6$, 90 MHz) δ 0.14 (s, 9H), 2.65 (br. t, J = ca. 6 Hz, 1H), 3.80 (m, 2H), 4.80 (t, J = 6.7 Hz, 1H), 7.2—7.7 (m, 5H); exact mass, 274.0294 (calcd for $C_{11}H_{18}O^{80}SeSi$, 274.0292).

1-(Tetrahydropyran-2-yloxy)-4-trimethylsilyl-4-pentene (41).[114] In a dry 500 mL three-necked flask equipped with reflux condenser, dropping funnel, vacuum take-off and magnetic stirring bar, dry magnesium turnings (3.940 g, 0.162 mol) were placed and the apparatus was alternately evacuated and filled with nitrogen (three times). Dry THF (45 mL) was then added by syringe, followed (magnetic stirring) by 1-bromo-1-trimethylsilylethylene[115] (21.3 g, 0.119 mol) in dry THF (10 mL) at such a rate that reflux was not too brisk (40 min). The resulting orange mixture was refluxed for a further 90 min and was then allowed to cool. The dropping funnel was quickly replaced, under a stream of nitrogen, with a rubber septum, and the Grignard solution was syphoned, by means of a dry, nitrogen filled, double ended needle, into another dry, nitrogen-filled, 500 mL three-necked flask. The latter flask was equipped with a vacuum take-off, two rubber septa and a magnetic stirring bar and contained a stirred and cooled (0°C) mixture of cuprous iodide (1.44 g, 7.60 mmol), 1-iodo-3-(tetrahydropyran-2-yloxy)propane[116] (20.50 g, 0.0759 mol) and dry THF (50 mL). The syphoning rate was controlled by adjusting the nitrogen pressure in such a way that the addition was rather slow (30 min). The flask originally containing the Grignard reagent was rinsed with portions of dry THF (3 x 10 mL) which were then syphoned into the second flask. The resulting black suspension was stirred overnight, during which time the cold bath attained room temperature. Aqueous saturated ammonium chloride (150 mL) was then cautiously added, the two-phase mixture was filtered through a Celite pad (5 x 3 cm) to remove the black deposit, and the pad was washed with ether (100 mL). The organic phase was separated, washed with brine (150 mL) and dried (Na_2SO_4). Evaporation left a green oil which appeared to be mainly a single product (TLC, silica, 1:12 ethyl acetate—heptane; VPC, DEGS, 140°C). Distillation (61—84°C, 0.05 mm) afforded (41) as an oil (15.42 g, 84%) of better than 98.5% purity (VPC, DEGS, 140°C): NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 9H), 1.4—1.9 (m, 8H) 2.22 (br. t, J = *ca*. 8 Hz, 2H), 3.2—3.6 (m, 2H), 3.65—3.95 (m, 2H), 4.48 (m, 1H), 5.28 (m, 1H), 5.54 (m, 1H).

4-Trimethylsilyl-4-penten-1-ol (30).[117]

1-(Tetrahydropyran-2-yloxy)-4-trimethylsilyl-4-pentene (1.737 g, 7.16 mmol) and *p*-toluenesulfonic acid (103 mg, 0.60 mmol) were dissolved in dry methanol (60 mL) and the solution was stirred under nitrogen for 2 h at room temperature. The solvent was then evaporated and the residue purified by flash chromatography over silica gel (4 x 18 cm) with 1:10 ethyl acetate—heptane, followed by Kugelrohr distillation (130°C, 10 mm) to give (30) (0.977 g, 86%) as a colorless liquid which was homogeneous by TLC (Silica, 1:10 ethyl acetate—heptane) and of better than 99.9% purity (VPC, DEGS, 150°C). (30) had IR (film) 3300, 3040, 1600, 1060 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 9H), 1.6—1.85 (m, 3H), 2.22 (br. t, J = *ca*. 7.5 Hz, 2H), 3.44 (t, J = 6.2 Hz, 2H), 5.26 (m, 1H), 5.48 (m, 1H); exact mass, 143.0895 [calcd for $C_7H_{15}OSi$ ($M-CH_3$), 143.0892]. Anal. Calcd for $C_8H_{18}OSi$: C, 60.69; H, 11.46. Found: C, 60.81; H, 11.28.

Treatment of 4-trimethylsilyl-4-penten-1-ol (30) with various electrophiles.

(a) A solution of benzeneselenenyl chloride (79.0 mg, 0.413 mmol) in dry THF (4 mL plus 1 mL rinse) was added over *ca*. 3 min to a stirred, cooled (-75°C) suspension of silver trifluoroacetate (120 mg, 0.543 mmol) and 4-trimethylsilyl-4-penten-1-ol (58.1 mg, 0.367 mmol) in dry THF (3 mL). After a further period of five min at -75°C, the bath was removed and the mixture was stirred for 60 h with protection from light. The suspension was filtered through a Celite pad (2 x 5 cm); the pad was washed with ether, and the filtrate was evaporated. Examination by TLC (silica, 1:10 ethyl acetate—heptane) showed a major UV-active component as well as some starting material (by comparison with an authentic sample). Purification was achieved by PLC (one silica gel plate, developed with 1:20 ethyl acetate—heptane), followed by Kugelrohr distillation (150°C, 2 mm), to give 2-phenylselenomethyl-2-trimethylsilyltetrahydrofuran (42) (32.6 mg, 28.3%) as a colorless oil. (42) had: IR (film) 3065, 3050, 1577, 1248 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 9H), 1.8—2.25 (m, 4H), 3.04 (d, J = 12.0 Hz, 1H), 3.42 (d, J = 12.0 Hz, 1H), 3.66 (br. q, 1H, collapses to d, J = 8.2 Hz upon irradiation at δ 2.05), 3.94 (br. q, 1H, collapses to d, J = 8.2 upon irradiation at δ 2.05); exact mass, 314.0600 (calcd for $C_{14}H_{22}O^{80}SeSi$, 314.0605). Anal. Calcd for $C_{14}H_{22}SiSeO$: C, 53.66; H, 7.08. Found: C, 53.81; H, 7.00

(b) With N-phenylselenophthalimide: N-phenylselenophthalimide[9j] (181.6 mg, 0.601 mmol) in chloroform (4 mL plus 1 x 2 mL rinse) was added dropwise over 10 min to a stirred and cooled (-75°C) solution of 4-trimethylsilyl-4-penten-1-ol (30) (73.2 mg, 0.463 mmol) and p-toluenesulfonic acid monohydrate (7 mg, 0.037 mmol) in dry chloroform (2.5 mL). After a further 10 min the bath was removed, the mixture allowed to obtain room temperature (*ca.* 30 min) and then monitoring by TLC (silica, 1:10 ethyl acetate—heptane) was started. Compound (42) and some starting material were immediately detected, but qualitatively no change was observed after stirring overnight at room temperatue. Evaporation, PLC (one plate of silica gel developed with 1:20 ethyl acetate—heptane), and Kugelrohr distillation (150°C, 2 mm) gave (42) (20.1 mg, 13.4%) as a colorless oil, pure by TLC (silica, 1:20 ethyl acetate—heptane) and identical (NMR, IR) with the sample prepared as in (a).

(c) With silver trifluoroacetate-benzeneselenenyl chloride-pyridine: Benzeneselenenyl chloride (530.4 mg, 2.77 mmol) in THF (2 mL plus 1 x 2 mL rinse) was slowly added (main portion over 10 min) to a stirred, cooled (-75°C) suspension of silver trifluoroacetate (670 mg, 3.03 mmol) in dry THF (5 mL). After a further five min 4-trimethylsilyl-4-penten-1-ol (30) (393.7 mg, 2.49 mmol) in THF (2 mL plus 2 x 1 mL rinse) was added quickly, followed, after five min, by dry pyridine (0.25 mL, 3.09 mmol). The cold bath was then removed and the mixture stirred at room temperature (TLC control). Once again some product and starting material were detected after a short period as streaking spots. After a total of 140 h at room temperature (protection from light) the mixture was qualitatively the same (TLC). Evaporation, and usual purification (2 PLC silica gel plates developed with 1:20 ethyl acetate—heptane, then Kugelrohr distillation, 120°, 0.03 mm) gave pure (42) (225 mg, 28.8%), as a colorless oil, identical (NMR, IR) with a sample prepared as in (a) or (b).

(d) With silver trifluoroacetate-benzeneselenenyl chloride-silica gel: Compound (30) (87.9 mg, 0.555 mmol) in THF (2 mL plus 1 mL rinse) was added quickly to a stirred, cooled (-75°C) suspension of silver trifluoroacetate (436.2 mg, 1.974 mmol) and dry silica (1.050 g) in dry

THF (4 mL). Immediately afterwards benzeneselenenyl chloride (223 mg, 1.164 mmol) in THF (2 mL plus 1 mL rinse) was added. The cold bath was removed and the mixture stirred at room temperature. After 40 h (protection from light), examination by TLC (silica, 1:20 ethyl acetate—heptane and 1:4 ethyl acetate—heptane) showed no (42), but mainly diphenyl diselenide, starting material, and several other components in traces.

(e) With iodine: Iodine (89 mg, 0.350 mmol) in ether (5 mL) was added to a two-phase mixture consisting of (30) (53.4 mg, 0.337 mmol) in ether (5 mL) and aqueous sodium hydrogen carbonate (0.5 M, 5 mL). Decolorization was noticeable after ca. 3 h and was complete in 18 h. The organic phase was separated, washed with brine (10 mL), dried (Na_2SO_4) and evaporated. The product (50.0 mg, 93.6%) was starting material, as shown by NMR and TLC (silica, 1:4 ethyl acetate—heptane) comparison with an authentic sample.

(f) With iodonium di-sym-collidine perchlorate:[55] Iodine (71.7 mg, 0.282 mmol) in chloroform (5 mL plus 1 mL rinse) was added to a stirred suspension of di-sym collidine silver perchlorate[55] (127.7 mg, 0.284 mmol) in dry chloroform (2 mL). A yellow precipitate (silver iodide) and a colorless supernatant, containing iodonium di-sym-collidine perchlorate[55] were produced. This mixture was immediately treated with (30) (40 mg, 0.257 mmol) in chloroform (2 mL plus 1 mL rinse). The mixture was stirred at room temperature with protection from light. Examination by TLC (silica, 1:3 ethyl acetate—heptane) failed to detect any product even after 120 h: starting material was the major substance detected.

(g) With N-bromosuccinimide:[52e] N-bromosuccinimide (80.0 mg, 0.449 mmol) in THF (2 mL plus 1 mL rinse) was added over 2 min to a cooled (0°C), stirred solution of (30) (56.3 mg, 0.356 mmol) in dry THF (3 mL) under nitrogen. After 2 h at 0°C the yellow mixture still contained much starting material. (TLC control: silica, 1:4 ethyl acetate—heptane) as well as several other components. The bath was removed, and the solution stirred 1 h, then the solvent was evaporated. The residue (NMR; TLC, above conditions) was a green, tarry, intractable mixture containing many substances.

(h) With m-chloroperbenzoic acid: m-Chloroperbenzoic acid (85% w/w, 296 mg, 1.45 mmol) in THF (2 mL plus 1 mL rinse) was added to a stirred solution of (30) (210 mg, 1.326 mmol) in THF (5 mL) and stirring was continued overnight at room temperature. The mixture was poured into ether (50 mL) and water (50 mL), and the organic phase was washed with aqueous saturated sodium hydrogen carbonate (3 x 25 mL), dried (Na_2SO_4) and evaporated. Flash chromatography over silica gel (3 x 17 cm) with 1:3 ethyl acetate—heptane, followed by Kugelrohr distillation (130°C, 10 mm) gave 2-hydroxymethyl-2-trimethylsilyl tetrahydrofuran (44) (161.5 mg, 70%): IR (film) 3440, 1050, 842 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 9H), 1.6—2.05 (m, 4H), 2.58 (br. s, 1H), 3.45 (d, J = 11.4 Hz, 1H), 3.58 (d, J = 11.4 Hz, 1H), 3.65—3.80 (m, 1H, collapsed to d, J = 8.4 Hz upon irradiation at δ 1.85), 3.80—3.95 (m, 1H, collapsed to d, J = 8.4 Hz upon irradiation at δ 1.85); NMR (DMSO-d_6, 100 MHz) δ 0.06 (s, 9H), 1.5—2.0 (m, 4H), 2.35 (d, J = 5.4 Hz, 2H), 2.4—2.9 (m, 2H), 4.47 (t, J = 5.5 Hz, 1H); exact mass, 174.1075 (calcd for $C_8H_{18}O_2Si$, 174.1074). Anal. Calcd for $C_8H_{18}O_2Si$: C, 55.12; H, 10.41. Found: C, 55.31; H, 10.16.

(D): Additions of cuprates to α,β-unsaturated aldehydes.

Preparation of the α,β-unsaturated aldehydes. Dienal (47) (Aldrich) was distilled before use (b.p. 120°C, 20 mm). The material was a mixture (NMR) of geometric isomers. (45),[61f] (46),[61g] (48),[82] (49),[61f] (50)[70a] were prepared by literature procedures. The compounds are rather unstable but can be stored for short periods (2—4 weeks) at -20°C under a nitrogen atmosphere. New aldehydes were made by general methods as follows:

Cycloheptylideneacetaldehyde (51). This compound was prepared by P. Beaulieu[93b] according to a general procedure reported in the literature.[61f]

(2-Methylcyclohexylidene)-2-propionaldehyde, (52). A literature method[61f] was followed with some modifications. 2-Trimethylsilylpropionaldehyde *tert*-butylimine[61f] (3.510 g, 18.94 mmol) was injected neat over 10 min to a stirred, cold (0°C) solution of LDA [from diisopropylamine (2.5 mL, 17.71 mmol) and butyllithium in hexane (1.40 M, 12.7 mL, 17.78 mmol)] in THF (60 mL). After a further 10 min at 0°C the mixture was cooled to -75°C and 2-methylcyclohexanone (1.307 g, 11.65 mmol) in THF (2 mL plus 2 x 1 mL rinse) was injected (main portion over about 3 min). The mixture was stirred overnight, during which period the cold bath attained room temperature. Water (20 mL) and enough oxalic acid dihydrate to bring the pH to 4.5 were added. The mixture was stirred for 50 min and then partitioned between ether (50 mL) and water (50 mL). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 x 50 mL) and with brine (50 mL) and was dried over anhydrous potassium carbonate. Filtration and evaporation gave the crude product in which the major impurity (ca. 15%, VPC) was the starting ketone. Flash chromatography over silica gel (4 x 20 cm) with hexane containing increasing amounts (0.5—1% v/v) of ethyl acetate followed by Kugelrohr distillation (145°C, 10 mm) gave (52) (892 mg, 50%) as a 1:1 mixture (NMR, 200 MHz) of E and Z isomers of better than 97% purity (VPC, DEGS, 150°C): IR (film) 2770, 1665 and 1612 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.11 (d, J = 7.20 Hz, 1.5H), 1.19 (d, J = 6.85 Hz, 1.5H), 1.29—2.03 (m, 9H), 2.18 (m, 1H), 2.63 (m, 0.5H), 3.05 (m, 0.5H), 3.33 (m, 0.5H), 3.79 (m, 0.5H), 10.15 (s, 0.5H), 10.20 (s, 0.5H); exact mass, 152.1202 (calcd for $C_{10}H_{16}O$, 152.1201).

For characterization a sample of the aldehyde was converted[118] into its 2,4-dinitrophenylhydrazone: mp 120°C and 158—159°C (from ethanol, double mp). Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.67; H, 6.17; N, 16.59.

[2-(4aβ,8aβ-4a-Methyldecahydronaphthylidene)]acetaldehyde, (53). A general procedure[61t] was followed: t-butyllithium in pentane (1.72 M, 14 mL, 24.2 mmol) was added to THF (30 mL) at -75°C and the solution was kept at this temperature. (Z)-1-Bromo-2-ethoxyethylene[61t] (1.820 g, 12.1 mmol) was injected neat over 5 min and THF (3 x 1 mL) was used to rinse all of the bromide into the t-butyllithium solution. After a further period of 30 min at -75°C, cis-4a-methyl-2-naphthalenone[119] (1.677 g, 10.09 mmol) in THF (5 mL plus 2 x 1 mL rinse) was added (main portion over 10 min).

The cold bath was left in place and, after 5 h, the reaction mixture had attained room temperature. The mixture was then cooled to 0°C, aqueous hydrochloric acid (10% v/v, 15 mL) was added, the cooling bath was removed, and the two-phase system was stirred vigorously for 15 min. The organic layer was removed, the aqueous phase was extracted with ether (50 mL) and the combined organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (4 x 25 cm) using hexane containing increasing amounts (2—5% v/v) of ethyl acetate followed by Kugelrohr distillation (130—135°C, 0.15 mm) afforded (53) (1.460 g, 75%) as a pure (TLC, silica, 1:20 ethyl acetate—hexane) 1:1 mixture (NMR, 200 MHz) of E and Z isomers.

IR (film) 2765, 1662, 1625 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.7—3.1 (m, 18H, incorporating s at δ 1.07), 5.4—5.8 (m, 1H), 9.85 (d, J = 3.5 Hz, 0.5H), 9.93 (d, J = 3.5 Hz, 0.5H); exact mass, 192.1513 (calcd for $C_{13}H_{20}O$, 192.1514).

For characterization a sample was converted[118] into its 2,4-dinitrophenylhydrazone: mp 131—134°C (from ethanol). Anal. Calcd for $C_{19}H_{24}N_4O_4$: C, 61.27; H, 6.50; N, 15.04. Found: C, 61.11; H, 6.42; N, 14.83.

General Procedures[120] for Reaction of α,β-Unsaturated Aldehydes with Cuprates.

(*A*) *$Me_5Cu_3Li_2$ in ether*. Purified cuprous iodide (3 mmol) was placed in a dry 50 mL 3-necked flask carrying a magnetic stirring bar. Two necks of the flask were closed by rubber septa and the other by a vacuum take-off equipped with a stopcock. The flask was alternately evacuated and filled with nitrogen (3 cycles) and dry ether (10 mL) was then injected. The slurry was stirred at *ca*. 0°C (ice bath) and commercial ethereal MeLi containing 5% LiCl, (*ca*. 1.8 M, 5 mmol) was injected over 2—3 min. A dark yellow precipitate of methyl copper was deposited and then dissolved. Five min after the end of the addition the colorless (or faintly yellow) solution was cooled to the specified temperature and the enal (1 mmol) in ether (1 mL plus 2 x 1 mL rinse) was added over 5 min. After the appropriate time the mixture was quenched as specified below.

(B) $Me_5Cu_3Li_2$ in ether-pentane. Cuprous iodide (3 mmol) in dry ether (5 mL) was treated at 0°C with MeLi (5 mmol) as described under (A) above. Five min after the end of the addition the cuprate solution was cooled to the specified temperature and dry pentane (15 mL) was injected. The enal (1 mmol) in ether (1 mL plus 2 x 1 mL rinse) was added as described in (A) and, after the appropriate time, the reaction mixture was quenched as specified below.

(C) Me_2CuLi in ether. Cuprous iodide (1.2 mmol) in dry ether (10 mL) was treated at 0°C with MeLi (2.4 mmol) as described under (A) above. Five min after the end of the addition the cuprate solution was cooled to the specified temperature and the enal (1 mmol) in ether (1 mL plus 2 x 1 mL rinse) was injected as in (A) and, after the appropriate time, the reaction mixture was quenched as specified below.

(D) Me_2CuLi in ether-pentane. Cuprous iodide (1.2 mmol) in dry ether (5 mL) was treated at 0°C with MeLi (2.4 mmol) as described in (A). Five min after the end of the addition the cuprate solution was cooled to the specified temperature and dry pentane (15 mL) was injected, followed by the enal (1 mmol) in ether (1 mL plus 2 x 1 mL rinse). The mixture was quenched after the appropriate time as described below.

Quenching Procedures.

(E) Acetic acid. After an appropriate time, the reaction mixture was cooled to -75°C and acetic acid (0.2 mL per mmol of MeLi used) was injected very quickly with vigorous stirring. The cold bath was removed (gas evolution) and, after *ca.* 5 min an excess (*ca.* 10 mL) of saturated aqueous ammonium chloride was added. The stirred mixture was allowed to reach room temperature (*ca.* 30 min) and the white precipitate was filtered off. The solid was washed with ether (30 mL) and water (30 mL) and the combined organic phases were washed with saturated aqueous sodium hydrogen carbonate (2 x 50 mL) and with brine (2 x 50 mL). The solution was dried (Na_2SO_4) and evaporated and the product was obtained by Kugelrohr distillation.

(F) Chlorotrimethylsilane. After completion of the conjugate addition the reaction mixture was cooled to -75°C and, for every mmol MeLi used, chlorotrimethylsilane (0.17 mL, 1.30 mmol) was added quickly, followed by triethylamine (0.20 mL, 1.43 mmol) and HMPA (0.12 mL). The cold bath was removed and the suspension was stirred vigorously for 40 min, during which time the mixture attained room temperature. An excess (10 mL) of saturated aqueous ammonium chloride was added cautiously and petroleum ether (bp 30—60°C, 30 mL) was also added. The mixture was filtered by suction through a filter paper to afford two clear phases, the aqueous one usually being blue. The organic layer was washed with saturated aqueous ammonium chloride solution (30 mL), with water (3 x 30 mL) (for removal of HMPA) and, finally, with brine (2 x 50 mL). The organic solution was dried (Na_2SO_4) and evaporated and the product was obtained by Kugelrohr distillation.

Reactions with $Me_5Cu_3Li_2$.

(1-Methylcyclohexyl)acetaldehyde (45a). Procedure (A) was followed using cyclohexylidene acetaldehyde (45) (427.9 mg, 3.445 mmol). The enal was added at -75°C to the solution of $Me_5Cu_3Li_2$ and the reaction mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -40°C over 1.5 h and the mixture was recooled to -75°C and quenched with acetic acid. Work-up and Kugelrohr distillation (125—130°C, 10 mm) gave (45a)[121] (435.9 mg, 90%) of better than 97% purity (VPC, DEGS, 120°C). The material contained 1% (VPC) of the 1,2-addition product, 1-cyclohexylidene-2-propanol, (45b).[122]

(45a) had: IR (film) 2715, 1710 cm^{-1}; NMR (CDCl$_3$, 200 MHz) δ 1.08 (s, 3H), 1.1—1.7 (m, 10H), 2.32 (d, J = 3.4 Hz, 2H), 9.83 (t, J = 3.4 Hz, 1H); exact mass 139.1122 [calcd for $C_9H_{15}O$ (M-H), 139.1122].

3,3-Dimethyloctanal (46a). The procedure for (45a) was followed using 3-methyl-2-octenal (46) (mixture of isomers, 143.1 mg, 1.02 mmol). Work-up and Kugelrohr distillation (115°C, 10 mm) gave (46a) (144.1 mg, 90.4%) of better than 99% purity (VPC, DEGS, 130°C). The 1,2-addition product was not detected (VPC). (46a) had: IR (film) 2720, 1720 cm^{-1}; NMR (CDCl$_3$, 200 MHz) δ 0.89 (br. t, J = 7.8 Hz, 3H), 1.04 (s, 6H), 1.1—1.5 (m, 8H), 2.27 (d, J = 3.25 Hz, 2H), 9.85 (t, J = 3.25 Hz, 1H); exact mass, 155.1435 [calcd for $C_{10}H_{19}O$ (M-H): 155.1436]. For characterization a sample of (46a) was converted[118] into its 2,4-dinitrophenylhydrazone: mp 96°C (from ethanol). Anal. Calcd for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.14; H, 7.21; N, 16.52.

3,3,7-Trimethyl-6-octenal (47a). Procedure (A) was followed using 3,7-dimethyl-2,6-octadienal (47) (mixture of isomers, 186.3 mg, 1.224 mmol). The enal was added at -75°C to the solution of $Me_5Cu_3Li_2$ and the reaction mixture was immediately allowed to warm to 0°C over 4 h. The mixture was then recooled to -75°C and quenched with acetic acid. Work-up and Kugelrohr distillation (70—80°C, 0.5 mm) gave (47a)[69j] (165.6 mg, 80.4%) of better than 98% purity (VPC, DEGS, 140°C). The 1,2-addition product was not detected (VPC, NMR). (47a) had: IR (film) 2715, 1710 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 6H), 1.25—1.45 (m, 2H), 1.59 (s, 3H), 1.68 (s, 3H), 1.96 (m, 2H), 2.27 (d, J = 3.5 Hz, 2H), 5.07 (m, 1H), 9.82 (t, J = 3.50 Hz, 1H); exact mass, 168.1508 (calcd for $C_{11}H_{20}O$, 168.1514).

[(2,3-Dimethyl-1-nonen-1-yl)oxy]trimethylsilane (48a). Procedure (A) was followed using 2-methyl-2-nonenal (48) (mixture of E and Z isomers, 126.1 mg, 0.818 mmol). The enal was added at -75°C to the solution of $Me_5Cu_3Li_2$ and the mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -20°C over 2 h and the mixture was recooled to -75°C and quenched by general procedure (F) with chlorotrimethylsilane. Work-up and Kugelrohr distillation (150°C, 10 mm) gave (48a)

(183.6 mg, 92.6%) of better than 98% purity (VPC, DEGS, 95°C). The material contained 1.5% of the 1,2-addition product, [(3-methyl-2-decen-yl)oxy]trimethylsilane, (48b), as judged by comparison (NMR, 200 MHz) with an authentic sample.[122] (48a) had: IR (film) 1673, 1166 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 9H), 0.86 (t, J = 7.5 Hz, 3H), 0.96 (d, J = 7.6 Hz, 3H), 1.05—1.5 (m, 10H), 1.50 (d, J = 1.5 Hz, 3H), 2.01 (m, 1H), 6.05 (m, 1H); exact mass, 242.2068 (calcd for $C_{14}H_{30}OSi$, 242.2066). Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.35; H, 12.47. Found: C, 69.61; H, 12.57.

{[2-(1-Methylcyclohexyl)-1-propen-yl]oxy}trimethylsilane (49a). Procedure (B) for reactions in ether—pentane was followed using 2-cyclohexylidenepropionaldehyde (49) (140.3 mg, 1.015 mmol). The enal was added at -50°C to the solution of $Me_5Cu_3Li_2$ and the reaction mixture was immediately allowed to warm to 0°C over 2 h. The mixture was kept at this temperature for a further 30 min, cooled to -75°C and quenched by general method (F) with chlorotrimethylsilane. Work-up and Kugelrohr distillation (140°C, 10 mm) gave (49a) (202.2 mg, 88.0%) of better than 99% purity (VPC, DEGS, 115°C). The 1,2-adduct (49b) was not detected (VPC). (49a) had: IR (film) 1675, 1252 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.16 (s, 9H), 0.94 (s, 3H), 1.1—1.7 (m, 13H, incorporating d, J = 1.5 Hz at δ 1.54, 3H), 6.11 (q, J = 1.5 Hz, 1H); exact mass, 226.1751 (calcd for $C_{13}H_{26}OSi$, 226.1753). Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.58. Found: C, 69.21; H, 11.65.

(1-Methylcycloheptyl)acetaldehyde (51a). Procedure (A) was followed using cycloheptylidene acetaldehyde (51) (60.7 mg, 0.439 mmol). The enal was added at -75°C to the solution of $Me_5Cu_3Li_2$ and the mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -20°C over 2 h and the mixture was recooled to -75°C and quenched by general method (E) with acetic acid. Work-up and Kugelrohr distillation (150°C, 10 mm) gave (51a) (60.1 mg, 88.8%). The material was contaminated by 5.5% of the 1,2-addition product, 1-cycloheptylidene-2-propanol, (51b), as judged by comparison (VPC, DEGS, 150°C; ^{1}H-NMR, 200 MHz) with an authentic sample.[122] (51a) had: NMR ($CDCl_3$, 200 MHz) δ 1.08 (s, 3H), 1.2—1.8 (m, 12H), 2.26 (d, J = 3.50 Hz, 2H), 9.80 (d, J = 3.50 Hz, 1H). For characterization the 2,4-dinitrophenylhydrazone was prepared:[118] mp 90—91°C (from ethanol). Anal. Calcd for $C_{16}H_{22}N_4O_4$: C, 57.47; H, 6.63, N, 16.76. Found: C, 57.49; H, 6.69; N, 16.87.

{[2-(1,2-Dimethylcyclohexyl)-1-propen-yl]oxy}trimethylsilane (52a) and {[3-(2-Methylcyclohexylidene)2-butyl]oxy}trimethylsilane (52b). Procedure (B) for reactions in ether—pentane was followed using 2-methylcyclohexylidene-2-propionaldehyde (52) (mixture of isomers, 114.3 mg, 0.751 mmol). The enal was added at -50°C to the solution of $Me_5Cu_3Li_2$ and the reaction mixture was immediately allowed to warm to 0°C over 1.5 h. The mixture was kept at this temperature for a further 30 min, cooled to -75°C, and quenched, by general method (F) with chlorotrimethylsilane. Work-up and Kugelrohr distillation (145°C, 10 mm) gave an oil (158.7 mg, 88.0%). The material consisted of (52a) and (52b) in the ratio 46:54 as judged by comparison (VPC, DEGS, 115°C; ^{1}H-NMR, 200 MHz) with an authentic sample of (52b).[122] The 1,4-addition product (52a) was a 1:3 mixture (NMR) of diastereoisomers having NMR ($CDCl_3$, 200 MHz) δ 0.158 and 0.162 (partially overlapping singlets, 9H overall), 0.65 (d, J = 6.8 Hz, 2.25H), 0.77 (d, J = 7.1 Hz, 0.75H), 0.90 (s, 2.25H), 1.17 (s, 0.75H), 1.18—1.6 (m, 12H, incorporating d, J = 1.5 Hz, at δ 1.55), 5.94 (q, J = 1.5 Hz, 0.25H), 6.08 (q, J = 1.5 Hz, 0.75H). For further characterization (52a) was converted[123] to the derived 2,4-dinitrophenylhydrazone: mp 111—118°C (from ethanol). Anal. Calcd for $C_{17}H_{24}N_4O_4$: C, 58.60; H, 6.94; N, 16.08. Found: C, 58.44; H, 6.90; N, 16.22.

[2-(4aβ,8aβ-2,4a-Dimethyldecahydronaphthalene)]acetaldehyde (53a). Procedure (A) was followed using [2-(4aβ,8aβ-4a-Methyldecahydronaphthylidene)]acetaldehyde (53) (mixture of isomers, 157.5 mg, 0.819 mmol). The enal was added at -75°C to the solution of $Me_5Cu_3Li_2$ and the reaction mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -20°C over 2 h and the mixture was recooled to -75°C and quenched by general procedure (E) with acetic acid. Work-up, flash chromatography over silica gel (2 x 18 cm) with 3:97 ethyl acetate—hexane and Kugelrohr distillation (140°C, 0.1 mm) gave (53a) (144.2 mg, 84.5%) as an apparently homogeneous (TLC, silica, 1:20 ethyl acetate—hexane) oil. Examination by VPC (FFAP, 210°C) showed two peaks (relative areas 1:19) corresponding to the two aldehydes epimeric at C-2. The crude reaction product (before chromatography) contained 2% of the 1,2-adduct, 1-(2-cis-4a-methyldecahydronaphthylidene)-2-propanol) (53b) as judged by comparison (VPC) with an authentic sample.[122] (53a) had: IR (film) 2720, 1715 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.75—1.95 (m, 21H, including sharp singlets at δ 1.01 and 1.10, 3H ca. each), 2.38 (d, J = 3.55 Hz, 2H), 9.83 (t, J = 3.55 Hz, 1H); exact mass, 208.1825 (calcd for $C_{14}H_{24}O$, 208.1827). For further characterization, (53a) was converted[118] into its 2,4-dinitrophenylhydrazone: mp 180—183°C (from ethanol).

Anal. Calcd for $C_{20}H_{28}N_4O_4$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.75; H, 7.34; N, 14.37.

Reactions with Me_2CuLi.

These reactions were run under the same thermal conditions as their counterparts with $Me_5Cu_3Li_2$ but using the general procedures given above for Me_2CuLi experiments. After work-up and distillation the relative amounts of 1,2- and 1,4-addition products were determined by VPC and/or NMR (200 MHz). In the latter case the integration was performed on conveniently separated signals that were chosen from the NMR spectra of the pure 1,2- (obtained by use of MeLi) and 1,4-adducts (obtained usually by use of $Me_5Cu_3Li_2$). In most cases the olefinic signal of the trimethylsilyl enol ether or the aldehyde proton signal were used for estimation of the 1,4-adducts and the signal for the proton(s) on the carbon bearing the hydroxyl group (typically at δ 4.5—5.0) for the 1,2-adducts. The values obtained were checked by integration of any other suitable sets of signals, including the singlets due to the trimethylsilyl groups, in which case a relaxation delay of 30 sec between scans was used to allow complete relaxation.

Reaction of cyclohexylideneacetaldehyde (45) with Me_2CuLi in ether. Procedure (C) was followed using cyclohexylideneacetaldehyde (45) (180 mg, 1.449 mmol). The enal was added at -75°C to the solution of Me_2CuLi and the reaction mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -40°C over 1.5 h, the cooling bath was then removed and the reaction was quenched by rapid injection of saturated aqueous ammonium chloride (10 mL) with stirring.[124] When the mixture had reached room temperature it was extracted with ether (2 x 30 mL) and the combined organic phase was washed with saturated aqueous sodium hydrogen carbonate (2 x 30 mL) and with brine (2 x 30 mL). The solution was dried (Na_2SO_4) and evaporated and the product (148.4 mg) was obtained by Kugelrohr distillation. The material consisted (NMR, 200 MHz) of starting enal and reaction product in the ratio of 1:10. The reaction product itself was comprised of (45a) and (45b)[122] in the ratio 87:13 (71% combined yield after correction for recovered starting material).

Reaction of 3-methyl-2-octenal (46) with Me_2CuLi in ether. Procedure (C) was followed using 3-methyl-2-octenal (46) (140.0 mg, 0.998 mmol) in ether. The enal was added at -75°C to the solution of Me_2CuLi and the reaction mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -40°C over 1.5 h and the mixture was recooled to -75°C and quenched by general procedure (E) with acetic acid. Work-up and Kugelrohr distillation gave a mixture of (46a) and (46b)[122] (140.9 mg total, 90.3%) in the ratio (NMR, 200 MHz) of 91.5:8.5.

Reaction of 3,3,7-trimethyl-6-octenal (47) with Me_2CuLi in ether. Procedure (C) was followed using 3,3,7-trimethyl-6-octenal (47) (mixture of isomers, 519.9 mg, 3.380 mmol). The enal was added at -75°C to the solution of Me_2CuLi and the mixture was immediately allowed to warm up so that it reached 0°C over 4 h. The mixture was then cooled to -75°C and quenched by general procedure (E) with acetic acid. Work-up and Kugelrohr distillation gave a mixture of (47a) and (47b)[69j] (445.9 mg, total 78.5%) in the ratio (NMR, 200 MHz) of 9:1. Flash chromatography over silica gel (3 x 17 cm) using heptane containing increasing amounts (5—10% v/v) of ethyl acetate, gave, after Kugelrohr distillation, (140°C, 12 mm) (47a) (391.1 mg, 68.9%) of better than 98% purity (VPC) and identical (IR; NMR, 200 MHz) with a sample made using $Me_5Cu_3Li_2$. The flash chromatography also gave (47b)[69j] [39.0 mg, 6.8%; after Kugelrohr distillation (150°C, 10 mm)] which was a mixture of E and Z isomers (NMR, 200 MHz) and was better than 95% pure (VPC). (47b) had: NMR ($CDCl_3$, 200 MHz) δ 1.0—2.2 (m, 15H, incorporating doublets at δ 1.22 and 1.23, J = 7 Hz, 3H overall), 4.4—4.7 (m, 1H), 6.0—6.3 (m, 2H); exact mass, 168.1502 (calcd for $C_{11}H_{20}O$, 168.1514).

Reaction of 2-methyl-2-nonenal (48) with Me_2CuLi in ether. Procedure (C) was followed using 2-methyl-2-nonenal (48) (mixture of isomers, 120.0 mg, 0.865 mmol). The enal was added at -75°C to the solution of Me_2CuLi and the mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -20°C over 2 h and the mixture was recooled to -75°C and quenched, by general procedure (F), with chlorotrimethylsilane. Work-up and Kugelrohr distillation gave a mixture (209.4 mg, 92.2%) consisting (VPC; NMR, 200 MHz) of (48a) and (48b)[122] in the ratio of 94.5:5.5

Reaction of 2-cyclohexylidenepropionaldehyde (49) with Me_2CuLi in ether-pentane. Procedure (D) for reactions in ether—pentane was followed using 2-cyclohexylidene-propionaldehyde (49) (120.0 mg, 0.865 mmol). The enal was added at -50°C to the solution of Me_2CuLi and the reaction mixture was immediately allowed to warm up to 0°C over 2 h. The mixture was kept at this temperature for a further 30 min, cooled to -75°C and quenched by general procedure (F) with chlorotrimethylsilane. Work-up and Kugelrohr distillation gave an oil (180.3 mg, 91.7%) of better than 99% purity (VPC, DEGS, 115°C). The material consisted (NMR, 200 MHz) of (49a) and (49b)[122] in the ratio of 80:20.

Reaction of cycloheptylideneacetaldehyde (51) with Me_2CuLi in ether. Procedure (C) was followed using cycloheptylideneacetaldehyde (51) (104.2 mg, 0.754 mmol) in ether. The enal was added at -75°C to the solution of Me_2CuLi and the mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -20°C over 2 h and the mixture was recooled to -75°C and quenched by general procedure (E) with acetic acid. Work-up and Kugelrohr distillation gave an oil (102.5 mg, 88.1%) of better than 97% purity (VPC, DEGS, 150°C). The material consisted (NMR, 200 MHz) of (51a) and (51b)[122] in the ratio of 83:17.

Reaction of 2-(2-methylcyclohexylidene)propionaldehyde (52) with Me_2CuLi in ether—pentane. Procedure (D) was followed using 2-(2-methylcyclohexylidene)propionaldehyde (52) (118.5 mg, 0.778 mmol). The enal was added at -50°C to the solution of Me_2CuLi and the reaction mixture was immediately allowed to warm to 0°C over 1.5 h. The mixture was kept at this temperature for a further 30 min, cooled to -75°C and quenched, by general method (F), with chlorotrimethylsilane. Work-up and Kugelrohr distillation gave a mixture (162.8 mg, 87.0%) of better than 99% purity (VPC, DEGS, 115°C). The material consisted (NMR, 200 MHz) of (52a) and (52b)[122] in the ratio of 48.5:51.5.

Reaction of [2-(4aβ,8aβ-4a-methyldecahydronaphthylidene)]-acetaldehyde (53) with Me_2CuLi in ether. Procedure (C) was followed using [2-(4aβ,8aβ-4a-methyldecahydronaphthylidene)] acetaldehyde (53) (146.5 mg, 0.762 mmol). The enal was added at -75°C to the solution of Me_3CuLi and the reaction mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -20°C over 2 h and the mixture was recooled to -75°C and quenched by general procedure (E) with acetic acid. Work-up and Kugelrohr distillation gave a mixture (144.1 mg, 90.8%) consisting (VPC) of (53a) and (53b)[122] in the ratio of 97.5:2.5 and small amounts of other materials. Flash chromatography over silica gel (2 x 18 cm) using 3:97 ethyl acetate—hexane and Kugelrohr distillation gave pure (VPC) (53a) (129.9 mg, 81.9%) consisting (VPC) of two diastereoisomers in the ratio of 94:6.

Reactions of 2-cyclopentylidenepropionaldehyde (50) with various copper reagents.

(i) Reaction with Me_2CuLi in ether. This reaction is described in the literature and gives[70a] (86% yield) a mixture of (50a) and (50b) in the ratio of 36:64.

(ii) Reaction with $Me_5Cu_3Li_2$ in ether. Procedure (A) was followed using 2-cyclopentylidenepropionaldehyde (50) (132.8 mg, 1.069 mmol). The enal was added at -50°C to the solution of $Me_5Cu_3Li_2$ and the mixture was stirred at this temperature for 30 min. The temperature was then allowed to rise to 0°C over 2 h and was maintained at 0°C for further 30 min. The mixture was recooled to -75°C and quenched, by general procedure (F), with chlorotrimethylsilane. Work-up and Kugelrohr distillation (120°C, 10 mm) gave an oil (194.2 mg, 95.5%) of better than 99% purity (VPC, DEGS, 100°C), consisting (NMR,[125] 200 MHz) of (50a) and (50b) in the ratio of 77.5:22.5.

(iii) Reaction with $Me_5Cu_3Li_2$ in ether—pentane. Procedure (B) was followed using 2-cyclopentylidenepropionaldehyde (50) (132.8 mg, 1.069 mmol). The enal was added at -50°C to the solution of $Me_5Cu_3Li_2$ and the mixture was stirred at this temperature for 30 min. The temperature was then allowed to rise to 0°C over 2 h and maintained at 0°C for a further 30 min. The mixture was recooled to -75°C and quenched by general procedure (F) with chlorotrimethylsilane. Work-up and Kugelrohr distillation (120°C, 10 mm) gave an oil (210.6 mg, 88%) of better than 99% purity (VPC, DEGS, 100°C) consisting (NMR, 200 MHz) of (50a) and (50b) in the ratio 85:15.

(iv) Reaction with Me_3CuLi_2[76d] in ether. Ethereal MeLi (2.1 M, 2.0 mL, 4.2 mmol) was injected slowly into a stirred and cooled (0°C) slurry of purified cuprous iodide (265.4 mg, 1.394 mmol) in ether (14 mL). The cuprate solution was cooled to -50°C and the enal (50) (173.4 mg, 1.396 mmol) in ether (1 mL plus 3 x 1 mL rinse) was added (main portion over 5 min). After the addition the mixture was kept for 30 min at -50°C. The temperature was then allowed to rise to 0°C over 2 h. The mixture was kept at this temperature for 30 min, recooled to -75°C, and quenched by general method (F) with chlorotrimethylsilane (0.6 mL), triethylamine (0.75 mL) and HMPA (0.4 mL). The cold bath was removed and the mixture was worked up in the usual way. Kugelrohr distillation (120°C, 10 mm) gave an oil (251.5 mg, 84.8%) of better than 99% purity (VPC, DEGS, 100°C), consisting (NMR, 200 MHz) of (50a) and (50b) in the ratio of 4:96.

Reaction with $Me_5Cu_3(MgBr)_2$[92] in ether. Ethereal MeLi (1.91 M, 0.58 mL, 1.1 mmol) was injected dropwise into a stirred and cooled (0°C) slurry of purified cuprous iodide (635 mg, 3.330 mmol) in ether (12 mL). Five min after the end of the addition the yellow suspension was cooled to -40°C and an ether solution of methylmagnesium bromide (2.74 M, 1.6 mL, 4.40 mmol) was added. The temperature was allowed to reach -10°C over 30 min and then lowered to -40°C again. The enal (136.5 mg, 1.10 mmol) in ether (1 mL plus 2 x 1 mL rinse) was injected (main portion over 4 min). The temperature was then allowed to rise to 0°C over 1 h and kept at 0°C for 30 min. The mixture was recooled to -75°C and quenched by general procedure (F) with chlorotrimethylsilane (0.7 mL), triethylamine (0.9 mL) and HMPA (0.45 mL). The cold bath was removed and the mixture was worked up in the usual way. Kugelrohr distillation (120°C, 10 mm) gave an oil (145.4 mg, 92%) consisting (NMR, 200 MHz) of (50a), (50b)[70a] and (50c)[122] in the ratio 4:1:95. Consequently, the amounts of 1,2- and 1,4-adducts are in the ratio of 96:4.

Reaction with Me_3Cu_2Li[83] in THF. Ethereal MeLi (1.91 M, 1.90 mL, 3.63 mmol) was injected dropwise into a stirred and cooled (0°C) slurry of purified cuprous iodide (461.0 mg, 2.420 mmol) in THF (15 mL). Ten min after the end of the addition the pale pink solution was cooled to -50°C. The enal (147.4 mg, 1.19 mmol) in THF (1 mL plus 2 x 1 mL rinse) was added (main portion added over 5 min). The temperature was then allowed to rise to 0°C over 1 h and kept at 0°C for 1 h. The mixture was recooled to -75°C and quenched by general procedure (F) with chlorotrimethylsilane (0.6 mL), triethylamine (0.75 mL), and HMPA (0.4 mL). The cold bath was removed and the mixture was worked up in the usual way. Kugelrohr distillation (120°C, 10 mm) afforded an oil (204.4 mg) consisting (DEGS, 100°C) of (50a) and (50b)[70a] in the ratio of 20:80 as well as two other unidentified substances. The latter accounted for *ca*. 50% of the total product (VPC, rel. peak areas).

Preparation of 1,2-Adducts.

1-Cyclohexylidene-2-propanol (45b). Ether (10 mL) was added to ethereal MeLi (1.52 M, 1.6 mL, 2.43 mmol). The solution was cooled to 0°C and cyclohexylideneacetaldehyde (45) (200 mg, 1.61 mmol) in ether (1 mL plus 2 x 1 mL rinse) was injected (main portion added over *ca*. 2 min). The mixture was stirred for 2 h at 0°C and the reaction was then quenched by addition of saturated aqueous ammonium chloride (20 mL). The product was extracted with ether and the solution was dried and evaporated. Kugelrohr distillation (140°C, 10 mm) of the residue gave (45b) (205.2 mg, 90.8%) as an oil of better than 98% purity (VPC, DEGS, 120°C). IR (film) 3300, 1668, 1050 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.22 (d, J = 6.8 Hz, 3H), 1.3—2.3 (m, 11H), 4.60 (m, 1H), 5.15 (m, 1H); exact mass 140.1199 (calcd for $C_9H_{16}O$, 140.1201). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.34; H, 11.40.

4-Methyl-3-nonen-2-ol (46b). The procedure for (45b) was followed using 3-methyl-2-octenal (46) (109 mg, 0.777 mmol) in ether (1 mL plus 2 x 1 mL rinse) and ethereal MeLi (1.52 M, 0.8 mL, 1.216 mmol) in ether (7 mL). Kugelrohr distillation (140°C, 10 mm) gave (46b) (108.7 mg, 87.5%) as a mixture (VPC, DEGS, 130°C) of E and Z isomers of better than 99% purity. IR (film) 3320, 1665, 1060 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7.5 Hz, 3H), 1.15—1.65 (m, 10H, incorporating d, J = 6.25 Hz at δ 1.22), 1.66 (d, J = 1.0 Hz, 2.25H), 1.68 (d, J = 1.0 Hz, 0.75H), 1.9—2.2 (m, 2H), 4.53 (m, 1H), 5.16 (m, 1H); exact mass, 156.1512 (calcd for $C_{10}H_{20}O$, 156.1514). Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.63; H, 12.86.

[(3-Methyl-3-decen-2-yl)oxy]trimethylsilane (48b). The procedure for (45b) was followed using 2-methyl-2-nonenal (48) (mixture of isomers, 553.6 mg, 3.589 mmol) in ether (3 mL plus 2 x 1 mL rinse) and ethereal MeLi (1.52 M, 3.55 mL, 5.396 mmol) in ether (10 mL). Kugelrohr distillation (150°C, 10 mm) gave 3-methyl-3-decen-2-ol (550 mg, 90%) as a homogeneous (TLC, silica, 1:5 ethyl acetate—hexane) oil. A portion (278.8 mg, 1.637 mmol) was dissolved in ether (10 mL) and chlorotrimethylsilane (0.25 mL) and triethylamine (0.28 mL) were added. The mixture was refluxed for 2 h, cooled, filtered through a pad (5 x 2 cm) of Celite and evaporated. Flash chromatography over silica gel (2 x 18 cm) using hexane containing increasing amounts (1—20% v/v) of ethyl acetate gave, after Kugelrohr distillation (140°, 10 mm), (48b) (101 mg, 25.4%) of better than 99% purity (VPC, DEGS, 95°C). The material was a mixture (NMR) of *E* and *Z* isomers in the ratio of 85:15. IR (film) 1080, 840 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 7.65H), 0.09 (s, 1.35H), 0.88 (br t, J = 6.7 Hz, 3H), 1.18 (d, J = 6.4 Hz, 0.45H), 1.20 (d, J = 6.4 Hz, 2.55H), 1.25—1.60 (m, 7H), 1.57 (d, J = 1.0 Hz, 2.55H), 1.67 (q, J = 1.2 Hz, 0.45 H), 1.98 (m, 2H), 4.16 (q, J = 6.4 Hz, 0.85H), 4.72 (q, J = 6.4 Hz, 0.15H), 5.06 (br t, J = 7.0 Hz, 0.15H), 5.32 (br t, J = 7.3 Hz, 0.85H); exact mass, 242.2064 (calcd for $C_{14}H_{30}OSi$, 242.2066). Anal. Calcd for $C_{14}H_{30}OSi$: C, 69.35; H, 12.47. Found: C, 69.07; H, 12.45.

The flash chromatography also afforded, after Kugelrohr distillation (150°C, 10 mm), 3-methyl-3-decen-2-ol (258.4 mg, 65.1%) as an apparently homogeneous (TLC, silica, 1:5 ethyl acetate—hexane) oil: NMR ($CDCl_3$, 200 MHz) δ 0.88 (br t, J = 6.7 Hz, 3H), 1.2—1.5 (m, 11H, incorporating doublets at δ 1.23, J = 6.4 Hz, _ca_. 2.5 H, and at δ 1.22, J = 6.4 Hz, _ca_. 0.5H), 1.62 (s, 2.55H), 1.70 (m, 0.45H), 2.00 (m, 3H), 4.18 (q, J = 6.4 Hz, 0.85H), 4.77 (q, J = 6.4 Hz, 0.15H), 5.17 (br t, J = 7.1 Hz, 0.15 H), 5.39 (br t, J = 7.0 Hz, 0.85H).

[(3-Cyclohexylidene-2-butyl)oxy]trimethylsilane (_49b_).

The procedure for (_45b_) was followed using 3-cyclohexylidene-2-propionaldehyde (_49_) (634.6 mg, 4.591 mmol) in ether (5 mL plus 2 x 1 mL rinse) and ethereal MeLi (1.52 M, 4.5 mL, 6.84 mmol) in ether (25 mL). Work-up, flash chromatography over silica gel (3 x 18 cm) using 1:10 ethyl acetate—hexane and Kugelrohr distillation (120°C, 0.3 mm) gave 3-cyclohexylidene-2-butanol (590 mg, 83.3%) as a homogeneous (TLC, silica, 1:10 ethyl acetate—hexane) oil. A portion (220 mg, 1.426 mmol) of this material was dissolved in ether (10 mL) and chlorotrimethylsilane (0.22 mL) and triethylamine (0.24 mL) were added. The mixture was refluxed for 2 h, cooled, filtered through a pad (5 x 2 cm) of Celite, and evaporated. Flash chromatography over silica gel (2 x 17 cm) using hexane containing increasing amounts (1—10% v/v) of ethyl acetate gave, after Kugelrohr distillation (110°C, 0.3 mm), (49b) (91 mg, 28.1%) of better than 99% purity (VPC, DEGS, 115°C). IR (film) 1078 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.07 (s, 9H), 1.14 (d, J = 6.3 Hz, 3H), 1.4—1.6 (m, 6H), 1.60 (s, 3H), 2.14 (m, 4H), 4.85 (q, J = 6.3 Hz, 1H); exact mass, 211.1516 [calcd for $C_{12}H_{23}OSi$ ($M-CH_3$), 211.1518]. Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.58. Found: C, 69.02; H, 11.41.

The flash chromatography also afforded, after Kugelrohr distillation (120°C, 0.3 mm), 3-cyclohexylidene-2-butanol (145 mg, 65.9%) as a homogeneous (TLC, silica, 1:10 ethyl acetate—hexane) oil: NMR ($CDCl_3$, 200 MHz) δ 1.21 (d, J = 6.4 Hz, 3H), 1.3—1.6 (m, 10H), 1.65 (s, 3H), 2.2—2.4 (m, 4H), 4.92 (q, J = 6.4 Hz, 1H).

3-Cyclopentylidene-2-butanol (50c). The procedure for (45b) was followed using 2-cyclopentylidenepropionaldehyde (50) (132.1 mg, 1.063 mmol) in ether (1 mL plus 2 x 1 mL rinse) and ethereal MeLi (1.80 M, 0.7 mL, 1.26 mmol) in ether (10 mL). Kugelrohr distillation (85°C, 0.5 mm) gave (50c) (131.7 mg, 88.3%) as a homogeneous (TLC, silica, 1:10 ethyl acetate—hexane) oil. IR (film) 3330, 1072 cm^{-1}; NMR ($CDCl_3$, 200 MHz), δ 1.20 (d, J = 6.8 Hz, 3H), 1.3—2.6 (m, 12H), 4.63 (q, J = 6.8 Hz, 1H); exact mass, 140.1202 (calcd for $C_9H_{16}O$, 140.1201). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.25; H, 11.58.

1-Cycloheptylidene-2-propanol (51b). The procedure for (45b) was followed using cycloheptylideneacetaldehyde (51) (246.5 mg, 1.784 mmol) in ether (1 mL plus 2 x 1 mL rinse) and ethereal MeLi (1.52 M, 1.80 mL, 2.736 mmol) in ether (15 mL). Work-up and flash chromatography over silica gel (2 x 20 cm) using 1:5 ethyl acetate—hexane followed by Kugelrohr distillation (110°C, 0.3 mm) gave (51b) (207 mg, 75.2%) as a homogeneous (TLC, silica, 1:5 ethyl acetate—hexane) oil of better than 99% purity (VPC, FFAP, 150°C). IR (film) 3330, 1652, 1053 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 1.23 (d, J = 6.0 Hz, 3H), 1.3—1.9 (m, 9H), 2.15—2.45 (m, 4H), 4.57 (m, 1H), 5.21 (m, 1H); exact mass, 154.1358 (calcd for $C_{10}H_{18}O$, 154.1358). Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.84; H, 11.67.

{[3(2-Methylcyclohexylidene)-2-butyl)oxy}trimethylsilane (52b). The procedure for (45b) was followed using (2-methylcyclohexylidene)-2-propionaldehyde (52) (787.0 mg, 5.177 mmol) in ether (5 mL plus 2 x 1 mL rinse) and ethereal MeLi (1.50 M, 6.9 mL, 10.35 mmol) in ether (25 mL). Kugelrohr distillation (110°C, 0.3 mm) gave 3-(2-methylcyclohexylidene)-2-butanol (761 mg, 87.5%) as a homogeneous (TLC, silica, 1:5 ethyl acetate—hexane) oil: NMR ($CDCl_3$, 200 MHz) δ 1.0—1.3 (series of 8 overlapping doublets, 6H overall), 1.3—3.2 (m, 12H), 4.80—5.05 (m, 1H). A portion (421.2 mg, 2.50 mmol) was dissolved in ether (10 mL) and chlorotrimethylsilane (0.38 mL) and triethylamine (0.42 mL) were added. The mixture was refluxed for 2 h and worked up as described for (49b). The crude product was purified by flash chromatography over silica gel (2 x 18 cm) using hexane containing increasing amounts of ethyl acetate (1—20% v/v). Kugelrohr distillation (160°C, 10 mm) gave (52b) (200.5 mg, 33.2%) of better than 98% purity (VPC, DEGS, 115°C). IR (film) 1252, 1085 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.088, 0.079, 0.044, 0.041 (four singlets, 9H overall), 0.95—1.2 (series of 8 overlapping doublets, 6H overall), 1.2—3.0 (m, 12H), 4.75—5.00 (m, 1H); exact mass, 240.1907 (calcd for $C_{14}H_{28}OSi$: 240.1909). Anal. Calcd for $C_{14}H_{28}OSi$: C, 69.93; H, 11.74. Found: C, 70.18; H, 11.84.

The flash chromatography also afforded, after Kugelrohr distillation, the starting alcohol (240.9 mg, 57.2%) as a homogeneous (TLC, silica, 1:4 ethyl acetate—hexane) oil.

[2-(4aβ,8aβ-4a-Methyldecahydronaphthylidene)]-2-propanol (53b). The procedure for (45b) was followed using (53) (148.2 mg, 0.771 mmol) in ether (1 mL plus 2 x 1 mL rinse) and ethereal MeLi (1.52 M, 0.75 mL, 1.156 mmol) in ether (10 mL). Work-up, flash chromatography over silica gel (2 x 18 cm) with 1:8 ethyl acetate—hexane and Kugelrohr distillation (160°C, 0.15 mm) gave (53b) (124 mg, 77.2%) as an apparently homogeneous (TLC, silica, 1:8 ethyl acetate—hexane) oil of better than 98% purity (VPC, FFAP, 210°C). The material was a mixture (NMR) of 4 diastereoisomers. IR (film) 3330, 1660, 1055 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 0.9—2.5 (m, 22H, incorporating 4 sharp doublets with J = 8 Hz at δ 1.240, 1.230, 1.222 and 1.220, and 2 singlets at δ 1.032 and 1.026, all of comparable intensity), 4.58 (m, 1H), 5.11 (br d, J = 8 Hz, 0.5H), 5.22 (br d, J = 8 Hz, 0.5H); exact mass, 208.1829 (calcd for $C_{14}H_{24}O$, 208.1827). Anal. Calcd for $C_{14}H_{24}O$: C, 80.70; H, 11.61. Found: C, 80.74; H, 11.54.

Reaction of cyclohexylideneacetaldehyde (45) with Me_2CuLi in ether—pentane. General procedure (D) was followed using (45) (136.3 mg, 1.098 mmol). The enal was added at -75°C to the solution of Me_2CuLi and the reaction mixture was stirred at this temperature for 2 h. The temperature was then allowed to rise to -40°C over 2 h, the cooling bath was removed, and the reaction was quenched by rapid injection of saturated aqueous ammonium chloride (10 mL) with stirring. Usual work-up and Kugelrohr distillation (130°C, 10 mm) gave a product (105 mg, 68.2%) that was comprised (NMR, 200 MHz) of (45a) and (45b) in the ratio 87:13.

Reaction of cyclohexylideneacetaldehyde (45) with $Me_5Cu_3Li_2$ (0.5 equivalents) in ether. Procedure (A) was used, except that only 0.5 equivalent $Me_5Cu_3Li_2$ were employed in ether (10 mL). Enal (45) (127.2 mg, 1.024 mmol) was added to the cooled (-75°C) solution of $Me_5Cu_3Li_2$ in ether. After 2 h at -75°C, the temperature was allowed to reach -40°C over 1.5 h, and then the mixture was quenched with aqueous saturated ammonium chloride (10 mL) and worked up as usual. Kugelrohr distillation gave the product (93.8 mg, 65%) comprised of (45a), (45b) and (45c) in a ratio (VPC, DEGS, 140°C, relative peak areas) 91.5:1.5:7. The ratio was confirmed by the NMR spectrum ($CDCl_3$, 100

MHz) of the mixture, in which the presence of (45c) was established by comparison with the spectrum of an authentic sample, prepared according to the literature.[61e]

Reactions of cyclohexylideneacetaldehyde (45) with methylcopper. To a stirred, cooled (0°C) slurry of cuprous iodide (570 mg, 2.99 mmol) in dry ether (15 mL) under a nitrogen atmosphere, methyllithium in ether (1.8 M, 1.50 mL, 3 mmol) was added over 5 min. The orange slurry was then cooled to -75°C and (45) (316.2 mg, 2.546 mmol) in ether (2 mL plus 2 x 1 mL rinse) was added (main portion over 5 min). The mixture was stirred at -75°C for 1 h, then the temperature was allowed to reach -10°C over 3 h, the bath removed, and saturated aqueous ammonium chloride (10 mL) was quickly injected. Usual work-up and distillation gave the product (232 mg, 54% corrected for recovery of starting material) comprised (NMR, 100 MHz) of unreacted (45) (50%), (45a) (33%) and (45c) (17%).

Decarbonylation attempts on (1-methylcyclohexyl)acetaldehyde (45a).

(i) A dry one-piece apparatus was used consisting of a 25 mL round-bottomed two-neck flask fused to a reflux condenser. The necks were fitted with rubber septa, and the flask contained a magnetic stirring bar. Tris(triphenylphosphine)-rhodium (I) chloride (656.0 mg, 0.709 mmol) was introduced. The system was alternately evacuated and filled with argon (3 cycles). Dry, degassed acetonitrile (15 mL) was injected, followed by (45a) (99.2 mg, 0.707 mmol) in acetonitrile (1 mL plus 2 x 1 mL rinse). The mixture was then stirred and refluxed under argon for 90 h. VPC was used to analyze the mixture (APIEZON L, 75°C for 2 min, then increased at a rate of 30°C/min to 150°C, n-decane as internal standard). 1,1-Dimethylcyclohexane (55) (identified by VPC comparison with a commercial authentic sample) was obtained in 9% yield. The starting material, (45a) was present in 80% yield.

(ii) The reaction was run in a similar way using tris(triphenylphosphine)rhodium (I) chloride (461.1 mg, 0.498 mmol), (1-methylcyclohexyl)acetaldehyde (45a) (179 mg, 1.276 mmol) in distilled, degassed benzonitrile (3 mL). After 16 h, VPC analysis revealed 20% yield (based on the rhodium reagent) of 1,1-dimethylcyclohexane (55) and 60% unreacted (45a) (APIEZON L, above conditions, *n*-decane as internal standard).

Reaction of 3-isobutyloxy-5,5-dimethyl-2-cyclohexen-1-one (56) with $Me_5Cu_3Li_2$.

General method (B) for reaction of enals with $Me_5Cu_3Li_2$ in ether—pentane was followed using 3-isobutyloxy-5,5-dimethyl-2-cyclohexen-1-one (56) (180.6 mg, 0.920 mmol). The enone was added to the cold (-50°C) solution of $Me_5Cu_3Li_2$ and the mixture was allowed to reach 0°C over 1.5 h, kept at 0°C for 30 min, and quenched with acetic acid according to procedure (E). Usual work-up and distillation (Kugelrohr, 95°C, 0.02 mm) gave unreacted (56) (170.9 mg, 95%), of better than 98% purity (VPC, DEGS, 170°C) and identical (NMR) with a sample of starting material.

Reaction of 1,3-cyclohexadiene monoepoxide (57)[126] with Me_2CuLi. To a stirred, cooled (0°C) slurry of cuprous iodide (622.8 mg, 3.270 mmol) in dry ether (10 mL), methyllithium in ether (1.56 M, 4.20 mL, 6.540 mmol) was added under nitrogen over 5 min and, after a further 5 min at 0°C, 1,3-cyclohexadiene monoepoxide (57)[126] (147.9 mg, 1.539 mmol) in ether (1 mL plus 2 x 1 mL rinse) was added over 5 min. After 30 min at 0°C, cold, saturated aqueous ammonium chloride was added (10 mL), followed by more ether (30 mL). The organic phase was separated, washed with brine (50 mL) and dried (Na_2SO_4). Evaporation and Kugelrohr distillation (120°C, 10 mm) gave the product (138.2 Mg, 80%) containing the known mixture[100] of 2-methyl-3-cyclohexen-1-ol (57b) (45%), 4-methyl-2-cyclohexen-1-ol (57a) (45%) and 3-cyclohexenone (57c) (10%), as shown by NMR ($CDCl_3$, 200 MHz) and VPC (DEGS, 120°C). The mixture had NMR ($CDCl_3$, 200 MHz) δ 0.95 (d, J = 7.0 Hz, 1.35 H), 1.08 (d, J = 6.2 Hz, 1.35H), 1.15—2.35 (m, 5.7H), 2.48 (m, 0.2H), 2.90 (m, 0.1H), 3.4 (m, 0.45H), 4.18 (m, 0.45H), 5.35—5.95 (m, 2H).

Reaction of 1,3-cyclohexadiene monoepoxide (57) with $Me_5Cu_3Li_2$. To a cold (0°C), stirred suspension of cuprous iodide (903.5 mg, 4.744 mmol) in dry ether (15 mL), methyllithium (1.56 M, 5.05 mL, 7.907 mmol) was added under nitrogen over 5 min and, after a further 5 min at 0°C, 1,3-cyclohexadiene monoepoxide (57) (143.5 mg, 1.493 mmol) in ether (1 mL plus 2 x 1 mL rinse) was added over 5 min. After 30 min, work-up as in the reaction with Me_2CuLi, followed by Kugelrohr distillation gave the product (131.8 mg, 79%), consisting (NMR, VPC, as above) of a 4.5:4.5:1 mixture of (57a), (57b) and (57c), respectively.

REFERENCES AND NOTES

1. See, for example, "The Alkaloids"; Grundon, M.F.; Senior Reporter, Specialist Periodical Reports; The Chemical Society: London, 1976; vol. 6.
2. Baldwin, J.E. *J. Chem. Soc., Chem. Commun*. 1976, 734.
3. a) See, for example, Horning, D.E.; Muchowski, J.M. *Can. J. Chem*. 1974; *52*, 1321 and references cited therein.

   b) Monkovic, I.; Conway, T.T.; Wong, H.; Perron, Y.G.; Pachter, I.J.; Belleau, B. *J. Am. Chem. Soc*. 1973, *95*, 7910.
4. a) Perie, J.J.; Laval, J.P.; Roussel, J.; Lattes, A. *Tetrahedron* 1972, *28*, 675.

   b) Roussel, J.; Perie, J.J.; Laval, J.P.; Lattes, A. *Tetrahedron* 1972, *28*, 701.
5. Methodology developed by Brown. See (a) Brown, H.C.; Geoghegan, P.J. Jr., *J. Am. Chem. Soc*. 1967, *89*, 1522. Also (b) Brown, H.C.; Geoghegan, P.J. Jr.; Kurek, J.T.; Lynch, G.J. *Organometal. in Chem. Synthesis* 1970, *1*, 7.
6. Perie, J.J.; Lattes, A. *Bull. Soc. Chim. Fr*. 1971, 1378.
7. Hegedus, L.S.; Allen, G.F.; Bozell, J.J.; Waterman, E.L. *J. Am. Chem. Soc*. 1978, *100*, 5800.

8. Purchased from Aldrich and used without further purification.

9. a) Clive, D.L.J.; Chittattu, G.; Curtis, N.J.; Kiel, W.A.; Wong, C.K. J. Chem. Soc., Chem. Commun. 1977, 725.

b) Clive, D.L.J.; Chittattu, G. J. Chem. Soc., Chem. Commun. 1977, 484.

c) Clive, D.L.J.; Russell, C.G.; Chittattu, G.; Singh, A. Tetrahedron 1980, 36, 1399.

d) Clive, D.L.J.; Chittattu, G.; Wong, C.K. Can. J. Chem. 1977, 55, 3894.

e) Clive, D.L.J.; Chittattu, G.; Wong, C.K. J. Chem. Soc., Chem. Commun. 1978, 441.

f) Nicolaou, K.C.; Lysenko, Z. J. Am. Chem. Soc. 1977, 99, 3185.

g) Nicolaou, K.C.; Seitz, S.P.; Sipio, W.J.; Blount, J.F. J. Am. Chem. Soc. 1979, 101, 3884.

h) Nicolaou, K.C.; Lysenko, Z. Tetrahedron Lett. 1977, 1257.

i) Nicolaou, K.C.; Barnette, W.E.; Magolda, R.L. J. Am. Chem. Soc. 1978, 100, 2567.

For the application of N-phenylselenophthalimide and N-phenylselenosuccinimide as carriers of the PhSe group (including one example of unsaturated urethane cyclization) see: (j) Nicolaou, K.C.; Claremon, D.A.; Barnette, W.E.; Seitz, S.P. J. Am. Chem. Soc. 1979,

101, 3704.

10. Clive, D.L.J.; Wong, C.K.; Kiel, W.A.; Menchen, S.M. J. Chem. Soc., Chem. Commun. 1978, 379.

11. Clive, D.L.J.; Chittattu, G.; Farina, V.; Kiel, W.A.; Menchen, S.M.; Russell, C.G.; Singh, A.; Wong, C.K.; Curtis, N.J. J. Am. Chem. Soc. 1980, 102, 4438.

12. a) Clive, D.L.J. J. Chem. Soc., Chem. Commun. 1973, 695.
    b) Sharpless, K.B.; Young, M.W.; Lauer, R.F. Tetrahedron Lett. 1973, 1979.
    c) Reich, H.J.; Reich, I.L.; Renga, J.M. J. Am. Chem. Soc. 1973, 95, 5813.
    In the specific case of β-phenylseleno urethanes, the fragmentation is expected to proceed specifically away from the nitrogen, to give allylic urethanes; see (d) Toshimitsu, A.; Owada, H.; Aoai, T.; Uemura, S.; Okano, M. J. Chem. Soc., Chem. Commun. 1981, 546.

13. For a discussion of the reaction and a comprehensive table of examples, see Clive, D.L.J. Tetrahedron 1978, 34, 1049.

14. Reich, H.J.; Chow, F.; Shah, S.K. J. Am. Chem. Soc. 1979, 101, 6638.

15. a) Reich, H.J.; Shah, S.K.; Chow, F. J. Am. Chem. Soc. 1979, 101, 6648. In our case, removal of the alkoxycarbonyl group might be necessary in order to prevent fragmentation. β-amino organolithium

compounds are known to fragment, but they can be prepared and used at low temperatures; see (b) Barluenga, J.; Fañanás, F.J.; Yus, M. J. Org. Chem. 1979, 44, 4798.

16. Sevrin, M.; Dumont, W.; Hevesi, L.; Krief, A. Tetrahedron Lett. 1976, 2647.

17. Okamura, H.; Miura, M.; Kosugi, K.; Takei, H. Tetrahedron Lett. 1980, 87.

18. For a typical procedure, see: Carter, H.E.; Frank, R.L.; Johnston, H.W. Org. Syn. Coll. Vol. III, 1953, 167.

19. Gibson, M.S.; Bradshaw, R.W. Angew. Chem. Int. Ed. 1968, 7, 919.

20. Kjær, A.; Jensen, R.B. Acta Chem. Scand. 1956, 10, 1365.

21. For a discussion see (a) House, H.O., "Modern Synthetic Reactions"; 2nd Ed., W.A. Benjamin: Menlo Park, Calif., 1972. For a recent refinement see (b) McMurry, J.E.; Musser, J.H. J. Org. Chem. 1975 40, 2556. For π-allyl palladium complexes as electrophiles with malonate anions, see: (c) Trost, B.M.; Fullerton, T.J. J. Am. Chem. Soc. 1973, 95, 8200. Also (d) Trost, B.M.; Stege, P.E. J. Am. Chem. Soc. 1977, 99, 1649. For recent methods of dealkoxycarboxylation see: (e) Krapcho, A.P.; Lovey, A.J. Tetrahedron Lett. 1973, 957.

(f) Kuo, Y.N.; Chen, F.; Ainsworth, C.; Bloomfield, J.J. *J. Chem. Soc., Chem. Commun*. 1971, 136.

22. We used the method by Pfeffer, P.E.; Silbert, L.S.; Chirinko, J.M., Jr. *J. Org. Chem*. 1972, *37*, 451.

23. We used the conditions of Erhardt, P.W. *J. Org. Chem*. 1979, *44*, 883. For a review of the reaction see Smith, P.A.S. *Org. Reactions* 1946, *3*, 337.

24. Use of diphenylazidophosphonate: (a) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* 1974, *30*, 2151. Trimethylsilylazide: (b) McMillan, J.H.; Washburne, S. *J. Org. Chem*. 1973, *38*, 2982. Pyridinium azide: (c) Van Reijendam, J.W.; Baardman, F. *Synthesis* 1973, 413. Tetrabuylammonium azide: (d) Brändström, A.; Lamm, B.; Palmertz, S. *Acta Chem. Scand*., 1974, *B28*, 699.

25. For a review on formation of carbon-carbon bonds via π-allyl nickel compounds, see Semmelhack, M.F. *Org. Reactions* 1972, *19*, 115.

26. Hurd, C.D.; Jenkins, W.W. *J. Org. Chem*. 1957, *22*, 1418.

27. (a) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* 1977 *60*, 978. See also (b) Baldwin, J.E.; Tzodikov, N.R. *J. Org. Chem*. 1977, *42*, 1978.

28. For a study on kinetic *vs*. thermodynamic addition of benzeneselenenyl halides to olefins, see: Raucher, S. *J. Org. Chem*. 1977, *42*, 2950.

29. a) Iler, R.K., "the chemistry of silica"; Wiley-Interscience: New York, 1979; p. 462.

b) There seems to be agreement that above 120°C most of the water adsorbed on the gel surface is lost, except the water contained in micropores. On further heating (up to 180°C) it is claimed that more tightly bound water molecules are also removed, although loss of silanol groups (with formation of siloxane bonds) appears to be significant, this leading presumably to a decrease in adsorption capability; see Iler, R.K., *op*. *cit*., pp. 622-59.

30. Grieco, P.A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* 1976, **41**, 1485.

31. In our particular case, i.e., (**15**) → (**1a**), the nitrogen is unlikely to participate because of the electron-withdrawing effect of the alkoxycarbonyl group, and so the ring size is unlikely to change during replacement of the OH group by PhSe.

32. See (a) Booth, H., in "Progress in Nuclear Magnetic Resonance"; Emsley, J.W.; Feeney, J.; Sutcliffe, L.H. Eds; Pergamon Press: Oxford 1969; vol. **5**, p. 162.

b) Anteunis, M. *Bull Soc. Chim. Belges* 1966, **75**, 413.

c) Abraham, R.J.; Parry, K.; Thomas, W.A. *J. Chem. Soc*. (B) 1971, 446. It is appreciated, however, that the proximity of electronegative substituents may have an effect on vicinal proton-proton coupling. There has been controversy on the subject (see Ref. 32a), but it seems established that in rather rigid cyclic systems (three- to five-membered) electronegative substituents having a lone pair aligned with one of the C-H sigma bonds involved in the coupling cause an increase in the absolute value of the coupling constant (see ref. 32b and 32c). The increase is especially marked for protons in a transoid relationship. In some five-membered ring amines J_{trans} is almost as large as J_{cis}, but derivatization of the nitrogen reduces markedly the effect, presumably by delocalizing the lone pair. These phenomena, however, do not affect our arguments, since a decrease in J_{cis} is not normally observed in systems with electronegative substituents. In fact, in (18), on the basis of decoupling experiments (see Experimental), the coupling constant between H_a and H_b is 7.5 Hz.

33. a) McConnell, J.G.; Blum, M.S.; Fales, H.M. Tetrahedron 1971, 27, 1129.
    b) CMR and mp of the derived hydrochloride were identical with the values described in (a) and 34.
34. Moriyama, Y.; Doan-Huynh, D.; Monneret, C.; Khuong-Huu, Q. Tetrahedron Lett. 1977, 825.

35. Experiments performed by Dr. A. Singh in this laboratory on the urethane derived from (**22**), under our conditions, show that in this case also the reaction proceeds with complete selectivity to yield the *cis* disubstituted product, although in rather poor yield. See Clive, D.L.J.; Farina, V.; Singh, A.; Wong, C.K.; Kiel, W.A.; Menchen, S.M. *J. Org. Chem*. 1980, **45**, 2120.

36. The trans dialkyl N-nitrosopiperidine would probably be the more stable isomer. See (a) Fuji, K.; Ichikawa, K.; Fujita, E. *J. Chem. Soc. Perkin I* 1980, 1066; also (b) Fraser, R.R.; Grindley, T.B. *Can. J. Chem*. 1975, **53**, 2465. For removal of the nitroso group see (c) Seebach, D.; Enders, D. *Angew. Chem. Int. Ed.* 1975, **14**, 15.

37. For example, it was not possible to rule out the presence of some (**26**) in these mixtures.

38. The purest sample of (**8a**) was obtained after quick column chromatography over silica gel, using dichloromethane [28% yield; composition (**8a**): 91%; (**8b**): 9%]. Alumina gave mainly starting material and low (<10%) yield of a 1:1 mixture of (**8a**) and (**8b**) (Experiments performed by W.A. Kiel).

39. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem*. 1978, **43**, 2923.

40. Posner, G.H. Angew. Chem. Int. Ed. 1978, 17, 487.

41. Cheer, C.J.; Johnson, C.R. J. Am. Chem. Soc. 1968, 90, 178.

42. See, for example Illuminati, G.; Mandolini, L. Acc. Chem. Res. 1981, 14, 95.

43. a) Jung, M.E.; Lyster, M.A. J. Chem. Soc., Chem. Commun. 1978, 315.
b) Olah, G.A.; Narang, S.C.; Gutpa, B.G.B.; Malhotra, R. J. Org. Chem. 1979, 44, 1247. Urethane (1a), however, was found to be inert to Me_3SiCl-NaI in acetonitrile: (c) Clive, D.L.J.; Kale, V.N. J. Org. Chem. 1981, 46, 231.

44. See Barton, J.W. in "Protective Groups in Organic Chemistry"; McOmie, J.F.W. Ed.; Plenum: London, 1973; p. 43.

45. For a review on the organic chemistry of silicon, see: (a) Fleming, I. in "Comprehensive Organic Chemistry"; Barton, D.H.R..; Ollis, W.D.; Eds.; Pergamon Press: Elmsford, N.Y., 1979; vol. 3, pp. 541-686. (b) Magnus, P. Aldrichimica Acta 1980, 13, 43.

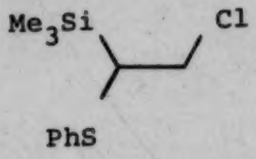
46. For example, a silicon-directed version of the Baeyer-Villiger oxidation has been described, see Hudrlik, P.F.; Hudrlik, A.M.; Nagendrappa, G.;

Yimenu, T.; Zellers, E.T.; Chin, E. J. Am. Chem. Soc. 1980, 102, 6894.

47. See Jarvie, A.W.P. Organomet. Chem. Rev., Sect. A 1970, 6, 153.

48. Reich, H.J.; Shah, S.K. J. Org. Chem. 1977, 42, 1773.

49. After the completion of this work, the reaction of vinylsilane (37) with benzenesulfenyl chloride to yield (i) has been described: Cooke, F.; Moerck, R.; Schwindemann, J.; Magnus, P. J. Org. Chem. 1980, 45, 1046.



(i)

The regiochemistry of the addition (and the lack of elimination) are consistent with our results and are rationalized in a similar way.

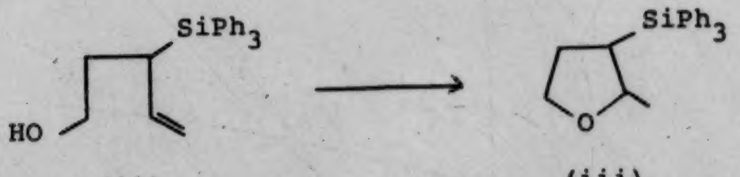
50. For the sulfur analogue, see ref. 49 and references cited therein.

51. Eaborn, C.; Jeffrey, J.C. J. Chem. Soc., 1954, 4266.

52. For a study of the acid catalyzed intermolecular ring opening of epoxysilanes see: (a) Hudrlik, P.F.; Hudrlik, A.M.; Rona, R.J.; Misra, R.N.; Withers, G.P. J. Am. Chem. Soc. 1977, 99, 1993. Also (b) Robbins, C.M.; Whitham, G.H. J. Chem. Soc., Chem. Commun. 1976, 697. For reaction of cuprates with epoxysilanes,

see: (c) Hudrlik, P.F.; Peterson, D.; Rona, R.J. J. Org. Chem. 1975, 40, 2263. For reactions with lithium aluminum hydride, see: (d) Eisch, J.J.; Trainor, J.T. J. Org. Chem. 1963, 28, 2870. For an example of intramolecular ring openings of epoxysilanes, see: (e) Ehlinger, E.; Magnus, P. J. Am. Chem. Soc. 1980, 102, 5004. The carbonyl oxygen atom has also been postulated as an intramolecular nucleophile for epoxysilanes: (f) Stork, G.; Jung, M.E. J. Am. Chem. Soc. 1974, 96, 3682.

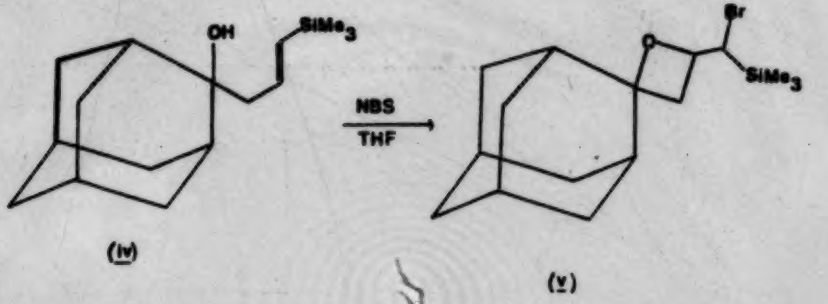
53. Allylsilane (ii) has been shown to cyclize smoothly to tetrahydrofuran (iii) simply during chromatography on acidic alumina (the regiochemistry is the one predicted by the β-effect):



(ii) (iii)

(52)

see Corriu, R.J.P.; Masse, J.; Samate, D. J. Organomet. Chem. 1975, 93, 71. A recent example of cyclization of a functionalized vinylsilane has been reported by Magnus [see eq. (53), ref. 52e].



(53) Here, however, the observed regiochemistry might be only a reflection of the fact that the alternative 5-endo closure is seriously hindered.[2]

54. Huynh, C.; Linstrumelle, G. Tetrahedron Lett. 1979, 1073 and references therein.

55. Lemieux, R.U.; Morgan, A.R. Can. J. Chem. 1965, 43, 2190.

56. It must be understood that the figures given for the coupling constants represent absolute values, the sign being presumably negative. For a useful compilation of geminal coupling constant data see (a) Cookson, R.C.; Crabb, T.A.; Frankel, J.J.; Hudec, J. Tetrahedron, 1966, Supplement 7, 355. (b) Chivers, P.J.; Crabb, T.A. Tetrahedron 1970, 26, 3389. The theory of geminal coupling is discussed in (c) Pople, J.A.; Bothner-By, A.A. J. Chem. Phys. 1965, 42, 1339. For a rationalization of the effect of vicinal heteroatoms on geminal coupling in 5- and 6-membered rings, see ref. 32b.

57. These arguments have been used to justify the observed α-opening in epoxysilanes: see Hudrlik, P.F.; Misra, R.N.; Withers, G.P.; Hudrlik, A.M.; Rona, R.J.; Arcoleo, J.P. Tetrahedron Lett. 1976, 1453.

58. Equilibration could occur under our experimental conditions, see (a) Clive, D.L.J. J. Chem. Soc., Chem. Commun. 1974, 100. (b) Reich, H.J. J. Org. Chem. 1974, 428. See also ref. 28.

59. See, for example R.B. Yeats in "Terpenoids and Steroids"; Overton, K.H.; Senior Reporter, Specialist Periodical Reports; The Chemical Society: London, 1979; vol. 9.

60. Other methodologies have appeared in the literature: use of aluminum alkyls, see (a) Jeffery, E.A.; Meisters, A.; Mole, T. Austr. J. Chem. 1974, 27, 2569. Use of cuprates with unsaturated sulfones, see (b) Posner, G.H.; Brunelle, D.J. J. Org. Chem. 1973, 38, 2747. From acetals, see (c) Bianchetti, G. Ann. Chim. (Roma) 1970, 60, 483. Use of alkyl titanium reagents, see (d) Reetz, M.T.; Westermann, J.; Steinbach, R. J. Chem. Soc., Chem. Commun. 1981, 237. Also (e) Reetz, M.T.; Westermann, J.; Steinbach, R. Angew Chem. Int. Ed. 1980, 19, 900. Use of cyclopropanes: see (f) Yamada, K.; Kyotani, Y.; Manabe, S.; Suzuki, M. Tetrahedron 1979, 35, 293.

(g) Oppolzer, W.; Godel, T. J. Am. Chem. Soc. 1978, 100, 2583.

61. For example, see: (a) Trippett; S.; Walker, D.M. Chem. Ind. 1960, 202. (b) Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. J. Org. Chem. 1973, 38, 36. (c) Meyers, A.I.; Munavu, R.; Durandetta, J. Tetrahedron Lett. 1972, 3929. (d) Meyers, A.I.; Tomioka, K.; Fleming, M.P. J. Org. Chem. 1978, 43, 3788. (e) Brink, M. Synthesis 1975, 253. (f) Corey, E.J.; Enders, D.; Bock, M.G. Tetrahedron Lett. 1976, 7. (g) Dauben, W.G.; Michno, D.M. J. Org. Chem. 1977, 42, 682. (h) Babler, J.H.; Coghlan, M.J. Synth. Commun. 1976, 6, 469. (i) Corey, E.J.; Enders, D. Chem. Ber. 1978, 111, 1362. (j) Rousseau, G.; Le Perchec, P.; Conia, J.M. Synthesis 1978, 67. (k) Trost, B.M.; Stanton, J.L. J. Am. Chem. Soc. 1975, 97, 4018. (ℓ) Cutting, I.; Parsons, P.J. Tetrahedron Lett. 1981, 2021. (m) Wittig, G.; Reiff, H. Angew. Chem. Int. Ed. 1968, 7, 7. (n) Takahashi, H.; Fujiwara, K.; Ohta, M. Bull. Chem. Soc. Jpn. 1962, 35, 1498. (o) Nagata, W.; Hayase, Y. J. Chem. Soc. C, 1969, 460. (p) Mukaiyama, T.; Hayashi, M. Chem. Lett. 1974, 15. (q) Mukaiyama, T.; Banno, K.; Narasaka, K. J. Am. Chem. Soc. 1974, 96, 7503. (r) Wollenberg, R.H.; Albizati, K.F.; Peries, R.

J. Am. Chem. Soc. 1977, 99, 7365. (s) Ficini, J.; Falou, S.; Touzin, A.M.; D'Angelo, J. Tetrahedron Lett. 1977, 3589. (t) Lau, K.S.Y.; Schlosser, M. J. Org. Chem. 1978, 43, 1595.

62. For decarbonylation of aldehydes, see: Tsuji, J.; Ohno, K. Synthesis 1969, 157.

63. See (a) Wakefield, B.S.: "The chemistry of organolithium compounds"; Pergamon Press: Oxford, 1974; p. 133. Also (b) Taschner, M.J.; Kraus, G.A. J. Org. Chem. 1978, 43, 4235.

64. (a) Milvalles, R.; Jacot-Guillarmot, A. Helv. Chim. Acta 1966, 49, 2313. (b) Cheminat, B. Bull. Soc. Chim. Fr. 1972, 3415. (c) Boccara, N.; Maitte, P. Bull. Soc. Chim. Fr. 1972, 1448.

65. (a) Gocmen, M.; Soussan, M.G.; Freon, P. Bull. Soc. Chim. Fr. 1972, 1448. (b) Gocmen, M.; Soussan, M.G. J. Organomet. Chem. 1973, 61, 19.

66. (a) McIntosh, J.M.; Khalil, H. Can. J. Chem. 1978, 56, 2134. (b) Kryshtal, G.V.; Kulganek, V.V.; Kucherov, V.F.; Yanovskaya, L.A. Synthesis 1979, 107. (c) Bonavent, G.; Causse, M.; Guitard, M; Fraisse-Jullien, R. Bull. Soc. Chim. Fr. 1964, 2462. (d) Marschall, H.; Vogel, F.; Weyerstahl, R. Tetrahedron Lett. 1976, 175. (e) Wartski, L.; El-Bouz, M.; Seyden-Penne, J. J. Organomet. Chem. 1979, 177, 17.

67. In fact, Corey has introduced a synthon equivalent to α,β-unsaturated aldehydes for the purpose of achieving conjugate additions: see Corey, E.J.; Boger, D.L. *Tetrahedron Lett*. 1978, 5; Corey, E.J.; Boger, D.L. *Tetrahedron Lett*. 1978, 9.

68. Posner, G.H. *Org. Reactions* 1972, *19*, 1.

69. See, for example (a) Boeckman, R.K., Jr.; Michalak, R. *J. Am. Chem. Soc*. 1974, *96*, 1623. (b) Andersen, N.H.; Ladner, D.W. *Synth. Commun*. 1978, *8*, 449. (c) Liu, H.-J.; Browne, E.N.C. *Can. J. Chem*. 1978, *56*, 306. (d) Trost, B.M.; Timko, J.M.; Stanton, J.L. *J. Chem. Soc., Chem. Commun*. 1978, 436. (e) Hansson, A.; Rahman, M.T.; Ullenius, C. *Acta Chem. Scand*. 1978, *32B*, 483. (f) Marino, J.P.; Floyd, D.M. *Tetrahedron Lett*. 1975, 3897. (g) Ager, D.J.; Fleming, I. *J. Chem. Soc., Chem. Commun*. 1978, 177. (h) Gustafsson, B. *Acta Chem. Scand*. 1977, *31B*, 382. (i) Bertz, S.H. *Tetrahedron Lett*. 1980, 3151. (j) Schwartz, M.; Wakabayashi, N.; Thing, E.G. *Org. Prep. and Proc. Int., Briefs* 1979, *11*, 97. (k) Boeckman, R.K., Jr.; Bruza, K.J.; Baldwin, J.E.; Lever, O.W., Jr. *J. Chem. Soc., Chem. Commun*. 1975, 519. (ℓ) Hamon, A.; Lacoume, B.; Olivier, A.; Pilgrim, W.R. *Tetrahedron Lett*. 1975, 4481.

70. (a) Chuit, C.; Foulon, J.P.; Normant, J.F. *Tetrahedron* 1980, *36*, 2305. (b) Chuit, C.; Foulon, J.P.; Normant, J.F. *Tetrahedron* 1981, *37*, 1385.

71. House, H.O.; Wilkins, J.M. *J. Org. Chem*. 1978, *43*, 2443.

72. House, H.O. *Acc. Chem. Res*. 1976, *9*, 59.

73. House, H.O.; Huber, L.E.; Umen, M.J. *J. Am. Chem. Soc*. 1972, *94*, 8471.

74. See, for example (a) Whitesides, G.M.; Kendall, P.W. *J. Org. Chem.* 1972, *37*, 3718. For a recent study, see: (b) Krauss, S.R.; Smith, S.G. *J. Am. Chem. Soc*. 1981, *103*, 141 and references therein.

75. House, H.O.; Chu, C.Y.; Wilkins, J.M.; Umen, M.J. *J. Org. Chem*. 1975, *40*, 1460.

76. (a) House, H.O.; Respess, W.L.; Whitesides, G.M. *J. Org. Chem*. 1966, *31*, 3128. (b) House, H.O.; Traficante, D.D. *J. Org. Chem*. 1963, *28*, 355. (c) House, H.O.; Traficante, D.D.; Evans, R.A. *J. Org. Chem*. 1963, *28*, 348. The reagent Me_3CuLi_2 does, however, add to ketones: see (d) Still, W.C.; McDonald, T.L. *Tetrahedron Lett*. 1976, 2659. (e) McDonald, T.L.; Still, W.C. *J. Am. Chem. Soc*. 1975, *97*, 5280.

77. (a) Posner, G.H.; Whitten, C.E.; McFarland, P.E. *J. Am. Chem. Soc*. 1972, *94*, 5106. (b) Barreiro, E.;

Luche, J.L.; Zweig, J.; Crabbè, P. Tetrahedron Lett. 1975, 2353.

78. See, for example, Ashby, E.C.; Bowers, J.R., Jr. J. Am. Chem. Soc. 1981, 103, 2242.

79. (a) House, H.O.; Snoble, K.A.J. J. Org. Chem. 1976, 41, 3076. (b) House, H.O.; Chu, C.Y. J. Org. Chem. 1976, 41, 3083.

80. Osborn, J.A.; Jardine, F.H.; Young, J.F.; Wilkinson, G. J. Chem. Soc. (A) 1966, 1711. See also ref. 62.

81. Shriner, R.L. Org. Reactions 1942, 1, 1.

82. Honwad, V.K.; Rao, A.S. Current Sci. (India) 1965, 34, 534.

83. Ashby, E.C.; Watkins, J.J. J. Am. Chem. Soc. 1977, 99, 5312.

84. Kauffman, G.B.; Teter, L.A. Inorg. Synth. 1963, 7, 9.

85. Ashby, E.C.; Lin, J.J.; Watkins, J.J. J. Org. Chem. 1977, 42, 1099.

86. Based on the hypothetical equation:

$$Me_5Cu_3Li_2 + 2R_1R_2C{=}CR_3CHO \rightarrow 2R_1R_2MeC\text{-}CR_3{=}CHOLi + 3MeCu \quad (54)$$

87. See ref. 77b and references cited therein.

88. For example, see (a) Van Rheenen, V. Tetrahedron Lett. 1969, 985. (b) Briggs, L.H.; Bartley, J.P.; Rutledge, P.S. Tetrahedron Lett. 1970, 1237.

89. Vollhardt, K.P.C.; Funk, R.L. J. Am. Chem. Soc. 1980, 102, 5253.

90. Methylenecyclopentane is less strained than cyclopentane (ca. 0.9 kcal/mole) while methylenecyclohexane is more strained than cyclohexane (0.55 kcal/mole); see Schleyer, P.v.R.; Williams, J.E.; Blanchard, K.R. J. Am. Chem. Soc. 1970, 92, 2377.

91. (a) See ref. 76a; also (b) Van Koten, G.; Noltes, J.G. J. Chem. Soc., Chem. Commun. 1972, 940. Lithium dimethylcuprate is dimeric in ether, but its structure has not been established: (c) Pearson, R.G.; Gregory, C.D. J. Am. Chem. Soc. 1976, 98, 4098. (d) San Filippo, J., Jr. Inorg. Chem. 1978, 17, 275.

92. Leyendecker, F.; Drouin, J.; Conia, J.M. Nouv. J. Chim. 1978, 2, 271.

93. (a) Clive, D.L.J.; Farina, V.; Beaulieu, P. J. Chem. Soc., Chem. Commun. 1981, 643. (b) Clive, D.L.J.; Farina, V.; Beaulieu, P. manuscript in preparation.

94. See Lemmle, J.; Ashby, E.C.; Roling, P.V. J. Org. Chem. 1973, 38, 2526, and references therein. Also Cieplak, A.S. J. Am. Chem. Soc. 1981, 103, 4540.

95. (a) Chérest, M.; Felkin, H. Tetrahedron Lett. 1968, 2205. (b) Chérest, M.; Felkin, H.; Frajerman, C. Tetrahedron Lett. 1971, 379. (c) Chérest, M.; Felkin, H. Tetrahedron Lett. 1971, 383.

96. See ref. 32a, page 231.

97. (a) Johnson, F.; Malhotra, S.K. *J. Am. Chem. Soc*. 1965, *87*, 5492. (b) Johnson, F.; Malhotra, S.K. *J. Am. Chem. Soc*. 1965, *87*, 5493. (c) Johnson, F.; Dix, D.T. *J. Am. Chem. Soc.* 1971, *93*, 5931.

98. For an example of unsuccessful use of Me$_2$CuLi due to steric hindrance, see Casares, A.; Maldonado, L.A. *Synth. Commun*. 1976, *6*, 11.

99. Martin, S.F. *Tetrahedron*, 1980, *36*, 419.

100. (a) Starosckik, J.; Rickborn, B. *J. Am. Chem. Soc*. 1971, *93*, 3046. (b) Wieland, D.M.; Johnson, C.R. J. Am. Chem. Soc. 1971, *93*, 3047.

101. See (a) Marino, J.P.; Hatanaka, N. *J. Org. Chem*. 1979, *44*, 4467. (b) Marino, J.P.; Floyd, D.M. *Tetrahedron Lett*. 1979, 675. See also (c) Wender, P.A.; Erhardt, J.M.; Letendre, L.J. *J. Am. Chem. Soc*. 1981, *103*, 2114.

102. Purchased from Chemical Dynamics Corporation, South Plain Field, New Jersey.

103. Kofron, W.G.; Baclawski, L.M. *J. Org. Chem*. 1976, *41*, 1879.

104. House, H.O.; Respess, W.L. *J. Organomet. Chem*. 1965, *4*, 95.

105. Kuivila, H.G.; Beumel, O.F. *J. Am. Chem. Soc*. 1961, *83*, 1246.

106. Korte, D.E.; Hegedus, L.S.; Wirth, R.K. *J. Org. Chem*. 1977, *42*, 1329.

107. Cristol, S.J.; Freeman, P.K. J. Am. Chem. Soc. 1961, 83, 4427.

108. Buu-Hoi, M.M.; Cagniant, P. Bull. Soc. Chim. Fr. 1945, 12, 978.

109. Laforge, F.B.; Green, N.; Gersdorff, W.A. J. Am. Chem. Soc. 1948, 70, 3707.

110. The evaporation and subsequent heating of the azide were done behind a safety shield. The apparatus was handled with large tongs and heavy asbestos gloves were worn.

111. (a) Wiegrebe, W.; Herrmann, E.-G.; Schlunegger, U.P.; Budzikiewicz, H. Helv. Chim. Acta 1974, 57, 301. (b) Karrer, P.; Portmann, P.; Suter, M. Helv. Chim. Acta 1948, 31, 1617.

112. Booth, H.; King, F.E.; Mason, K.G.; Parrick, J.; Whitehead, R.L. St. D. J. Chem. Soc. 1959, 1050.

113. Conditions described in ref. 58a.

114. Conditions are similar to those described in ref. 54.

115. (a) Sommer, L.H.; Bailey, D.L.; Goldberg, G.M.; Buck, C.E.; Bye, T.S.; Evans, F.J.; Whitmore, F.C. J. Am. Chem. Soc. 1954, 76, 1613. (b) Ottolenghi, A.; Fridkin, M.; Zilkha, A. Can. J. Chem. 1963, 41, 2977.

116. Hodgson, G.L.; McSweeney, D.F.; Money, T. J. Chem. Soc. Perkin I 1973, 2113.

117. Deprotection method: Corey, E.J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett*. 1976, 809.

118. Vogel, A.I., "Practical Organic Chemistry"; 3rd Ed., Longmans, Green and Co.: London, 1956; p. 344.

119. Yanagita, M.; Yamakawa, K. *J. Org. Chem*. 1957, **22**, 291.

120. When reactions were carried out on a different scale, amounts of reagents, volume of solvents and quenching agents were changed accordingly.

121. Burgstahler, A.W.; Nordin, I.C. *J. Am. Chem. Soc*. 1961, **83**, 198.

122. For the preparation and characterization of 1,2 adducts see p. 141.

123. Treatment of a mixture of (**52a**) and (**52b**) according to ref. 118 resulted in rapid hydrolysis of (**52a**), followed by precipitation of the required 2,4-DNP.

124. Subsequently this quenching procedure was found unsatisfactory and in the other cases acetic acid was employed, resulting in higher yields.

125. The following signals were compared: olefinic signal of (**50a**) (δ 6.09, q, J = 2 Hz) and methine signal of (**50b**) (δ 4.57, q, J = 6.4 Hz).

126. Crandall, J.K.; Banks, D.B.; Colyer, R.A.; Watkins, R.J.; Arrington, J.P. *J. Org. Chem*. 1968, **33**, 423.